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GASTRIC MOTILITY IN INFANTS AS SHOWN BY THE ROENTGEN RAY *

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The study of the stomach from radiographs, taken at frequent intervals after the introduction of bismuth in the regular feeding, offers a new and interesting method of observing gastric motility in infants. It is a subject which has a very important bearing on many of the questions which arise in connection with infant feeding, but we have at present very little accurate knowledge either of normal or abnormal motility in the gastric digestion of infants, as shown by this method of investigation.

The prevailing view expressed in text-books is that the infant's stomach empties itself in about two hours in breast-fed babies, and in three hours in artificially-fed babies. This opinion has been based on the results of the examination of the stomach contents obtained by siphonage.

Dr. Walter B. Cannon of Harvard was one of the first to study in animals gastric motility by means of the fluoroscope. With his work all are, doubtless, quite familiar. He showed that an acid reaction of the contents of the pyloric region of the stomach causes the pylorus to open, while an acid reaction in the duodenum causes it to remain closed. After the coagulation of the casein of milk the whey is readily acidified and passes the pylorus first, together with the carbohydrates. As the protein requires a longer time to combine with the acid of the stomach, it is some time before free acid is present, and its exit from the stomach is therefore delayed. The fatty acids and neutral fats are the last to pass the pylorus, because of the longer time required for the fatty acids to be neutralized by the duodenal secretions; and the pylorus, therefore, remains closed because of duodenal acidity. The opening and closing of the pylorus, according to this investigation, depend chiefly on the reaction of the gastric contents, which is the most vital factor in the motor activity of the stomach.

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The problem of studying gastric motility in infants is complicated by the many factors which enter into the composition of the food. Milk being the basis of the food, we have to start with a mixture of fats, sugar and proteins. The proteins are further of two kinds, part coagulable, part non-coagulable. In substitute feeding the percentages of these

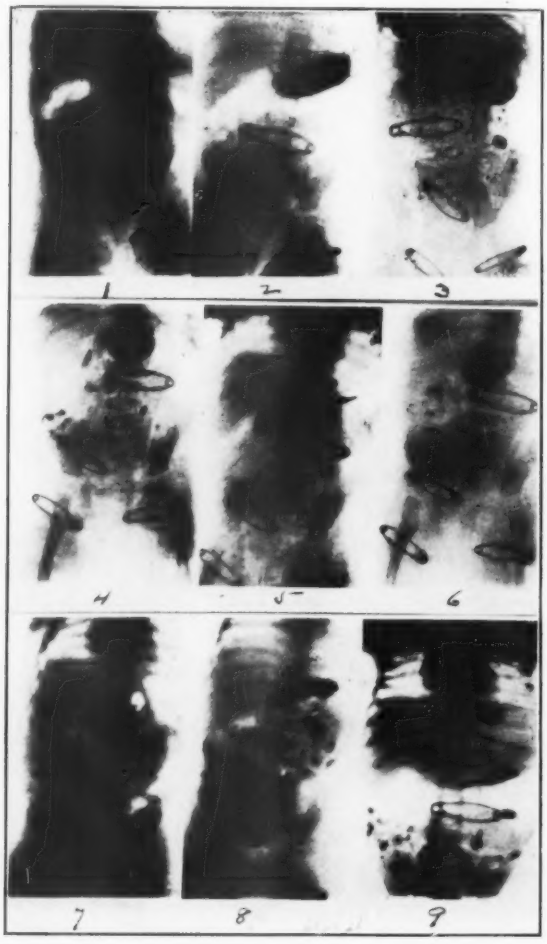

Fig. 1.—Series of radiographs illustrating gastric motility in the case of infant Laffey, 7 months old, breast fed, showing no disturbance of digestion.

various ingredients of milk are capable of indefinite variations, and one must bear in mind the possibility that within certain limits, different clinical results are obtainable by different percentage modifications. Furthermore, in substitute feeding, there are additional factors to be considered, such as (1) the acidity of the milk from normal or abnormal acid fermentation, (2) the changed reaction due to the practice of adding

alkalies, such as lime water, or bicarbonate of soda; (3) the use of cereal decoctions, such as that of barley, to break up the protein curd, or to supply a new food element, that is starch; (4) the use of the lactic acid mixtures and the various forms of precipitated caseins; (5) the use of other forms of sugar than that of milk, such as dextrimaltose and cane sugar.

In addition to such factors as I have enumerated, pertaining to the composition of milk, there are other conditions which may influence digestion and motility, such as the amount of food administered and the intervals between feedings. Variations in motility which might at first

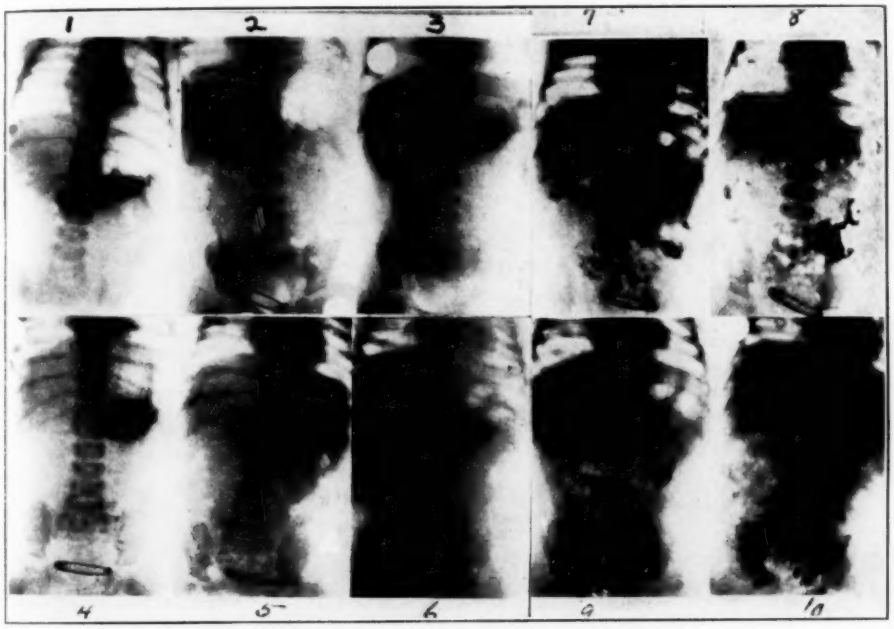

Fig. 2.—Radiographs in the case of infant Marsh, 10 months old, illustrating gastric motility.

be thought to be due to the composition of the food, may, in fact, be due to different effects on peristalsis produced by variations in amounts, which are either within or in excess of the gastric capacity of the infants under observation.

We must also inquire as to what happens to the residue in an incompletely emptied stomach when a new feeding is introduced: Does it mix intimately with the new food, or does it, under the influence of the peristalsis excited by the renewed distention of the stomach, pass out of the pylorus more rapidly than the new feeding?

In our work we have made no use of fluoroscopic examinations; partly because of the difficulty of making accurate records, but principally

because of the danger of burns from repeated prolonged exposures to the rays. We have in each series taken plates at intervals of one-half to one hour during the period of the experiment. It would have been more interesting to have had records at ten-minute intervals, during the full period of digestion, but this would have greatly increasel the expense and made an unreasonable tax on the time of the Roentgenologists at the hospital.

We have used the subcarbonate of bismuth in all our studies. The amount given has gradually been increased as no ill effects followed its administration, so that it is now our custom to give two rounded tea-

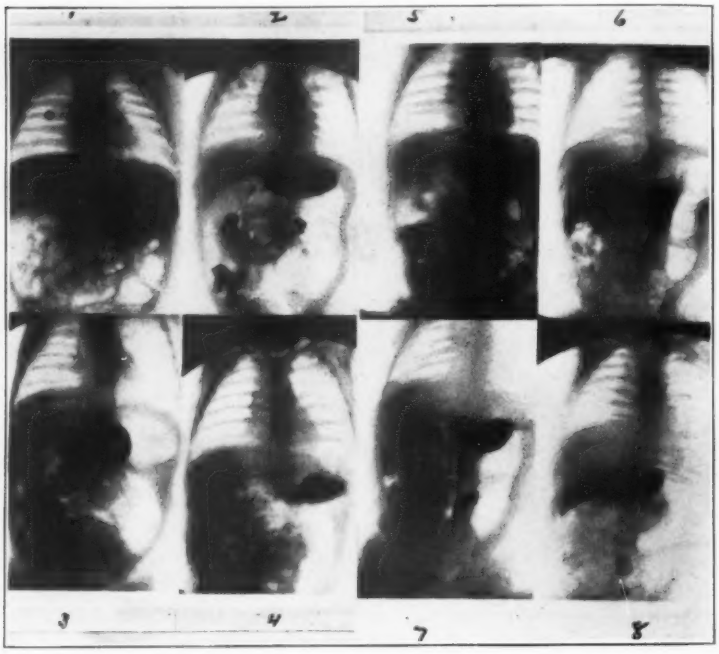

Fig. 3.—Radiographs in the case of infant Siglos, aged 4½ months, illustrating gastric motility as described in text.

spoonfuls at a single dose. The most satisfactory way of giving it is to mix it with an ounce of the milk which is introduced into the stomach with a tube, while another ounce of the milk is used to wash the bismuth down. The remainder of the feeding is then given through the nipple. This procedure is safe and gives the most uniform results. We have shown that the amount of bismuth, at least up to the maximum dose I have mentioned, does not influence the emptying time of the stomach. In from eight to ten hours after the beginning of the feeding the child generally has one or two bismuth stools, after which the stools regain

their normal color. Single large doses of the subcarbonate of bismuth do not seem to cause constipation or any other ill effect.

It is obvious that in work of this sort many cases must be studied before one can draw reliable conclusions as to the results. My cases are still few in number and ideas in regard to the significance of the facts which have been observed may have to be modified in the light of further investigations. I have based my observations on about fourteen cases, or twenty-four series, with about one hundred and twenty-four plates.

1. One of the most striking things observed is the curious lack of peristalsis to be seen in infants' stomachs as compared with adults.

2. Only twice have I been able to show the outline of the duodenum distinctly. The reason for this is not clear, unless it is that the food remains in the duodenum only a short time, and that the plates were taken at such long intervals, comparatively, that the duodenal stage was missed.

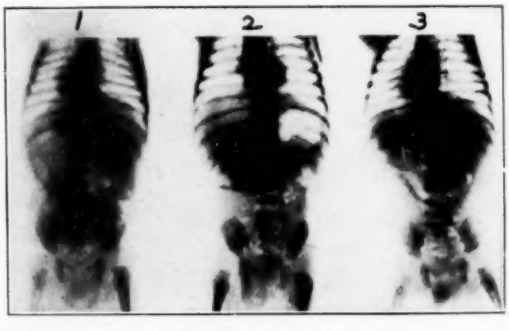

Fig. 4.—Illustrating gastric motility in infant Gillis before operation.

3. In a case of normal digestion, if the plate is clear-cut, bismuth appears in the small intestines as soon as the feeding is completed, showing that a considerable amount of food passes into the duodenum without undergoing gastric digestion.

4. The stomach appears to empty itself of the greater part of its contents in from one and one-half to two and one-half hours, the emptying process being more rapid in some cases than in others.

After the greater part of the stomach contents has passed into the small intestines, a considerable residue remains, which is emptied very slowly, often remaining for four and one-half to five or even seven and one-half hours, in both breast-fed and bottle-fed babies.

5. When a bismuth feeding is given and another feeding follows at the end of the regular two and one-half or three hour interval, the bismuth residue from the first feeding does not appear to mix intimately

with the new feeding, but, as a rule, passes out into the small intestines much more quickly than it does when left to itself. The suggestion is strong that the distention of the stomach by a new feeding, if not excessive, stimulates peristalsis and favors the expulsion of the bismuth residue into the duodenum. On the other hand, if the distention is excessive, peristalsis may be inhibited and the emptying time of the stomach delayed.

6. In congenital pyloric stenosis the dilatation and peristalsis is marked; the pyloric end showing the same prow-like formation seen in

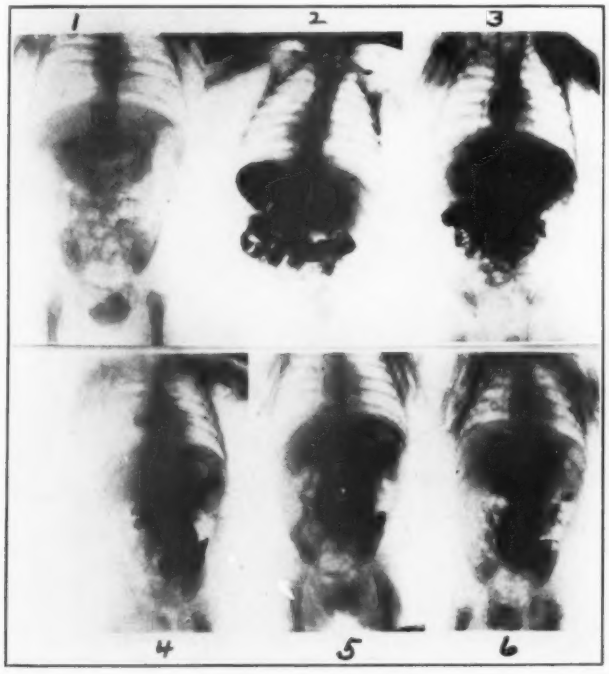

Fig. 5.—Illustrating gastric motility in infant Gillis after operation.

adults. After a posterior gastro-enterostomy the stomach appears to expel its contents through the artificial opening quite as rapidly, if not more so, than in the normal stomach.

7. As the opening of the pylorus is dependent on the secretion of hydrochloric acid in the stomach, the early appearance of bismuth in the intestines and the expulsion of the major part of the contents within two hours would suggest that the bismuth does not of itself interfere with the normal motility of the organ. Moreover, the plates show in one series that the bismuth had disappeared from the stomach, in one experiment in two and one-half hours, in another in seven and one-half

hours — the difference in the emptying time being due presumably to differences in the composition of the food, the amount of bismuth being the same in both cases.

It is not practical to reproduce all the plates which were taken and on which my observations were based. The following are fairly illustrative.

Figure 1.—Laffey. A child 7 months old, breast-fed, showing no disturbance of digestion. The child was allowed to nurse for a few minutes and was then given about 200 grains of bismuth mixed with breast-milk and then allowed to nurse from the breast for the remaining twenty minutes. The plates were nine in number, the first immediately

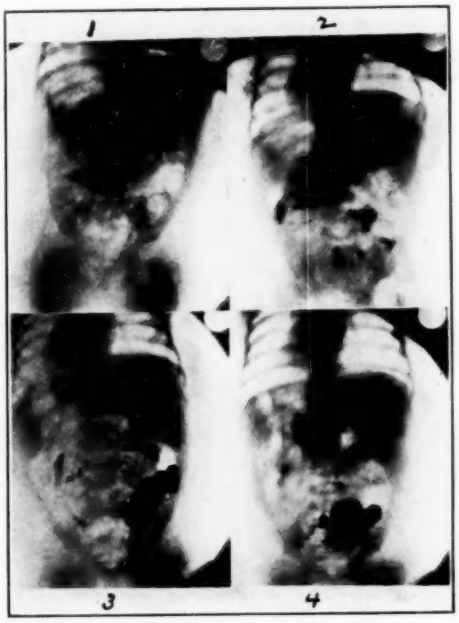

Fig. 6. Radiographs in the case of infant Randolph, breast fed, aged 6½ months. This and figures 7, 8, 9, 10 and 11 represent an attempt to study systematically the effect of foods of different composition in the same baby.

after the feeding, the next five at thirty minute intervals and the last three at one-hour intervals. The small amount of food remaining in the stomach is shown in No. 3, made one and one-half hours after the beginning of the feeding. In the remaining plates, covering a period of four and one-half hours, the slow rate at which the food was expelled from the stomach is shown; there still remained a small amount in the last plate, taken about six hours after the beginning of the feeding.

Figure 2.—Marsh. An infant, 10 months old, weighing 19 pounds and 11 ounces. It was given 7 ounces of a prescription calling for 3 per

cent. fat, 7 per cent. maltose, 2 per cent. protein, 0.75 per cent. of barley starch, with 150 grains of bismuth subcarbonate. The plates, ten in number, were taken at thirty-minute intervals. In No. 9, the stomach, five hours after the beginning of the feeding, still shows a small bismuth residue. Immediately afterward, a feeding without bismuth was given. No. 10, taken thirty minutes after No. 9, shows no bismuth in the stomach, the residue having been expelled, presumably under the influence of the peristalsis excited by the new feeding, which was given immediately after No. 9 was taken. In this case, as in that of Laffey, one sees in No. 4 the rapid emptying of the major part of the stomach

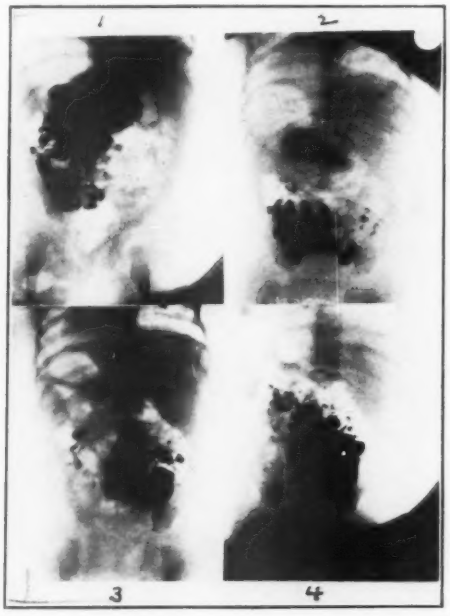

Fig. 7.—Infant Randolph, February 5. For description see Figure 6.

contents in two hours after the beginning of the feeding, and also one observes the very slow expulsion of the food in Nos. 4 to 9, representing a period of three hours.

No. 8 in the Laffey series and Nos. 8 and 9 in the Marsh series show an unusual form to the bismuth residue and may possibly represent a spasm of the stomach, as both babies were crying vigorously from hunger at the time.

Figure 3.—Siglos. Infant, aged 4½ months, weighing 13 pounds and 12 ounces. The feeding was 2 ounces of whole milk and 2 ounces of barley water with one teaspoonful of cane sugar and about 200 grams of bismuth. In a series, the plates of which are not reproduced here, the stomach was emptied of its contents in three to three and one-half

hours. In the second series, the same feeding was given and two hours later, about one hour before the feeding was due, a second feeding was given to see what effect was produced on the emptying time of the stomach by overcrowding the feeding. The result is very interesting. The first radiograph, immediately after the feeding, shows the fully distended stomach; No. 2, taken two hours later, shows how large a part of the feeding has passed into the intestines. No. 3 shows the condition immediately after the new feeding, illustrating very well how little the residue from the previous feeding mixes with the new feeding. No. 4

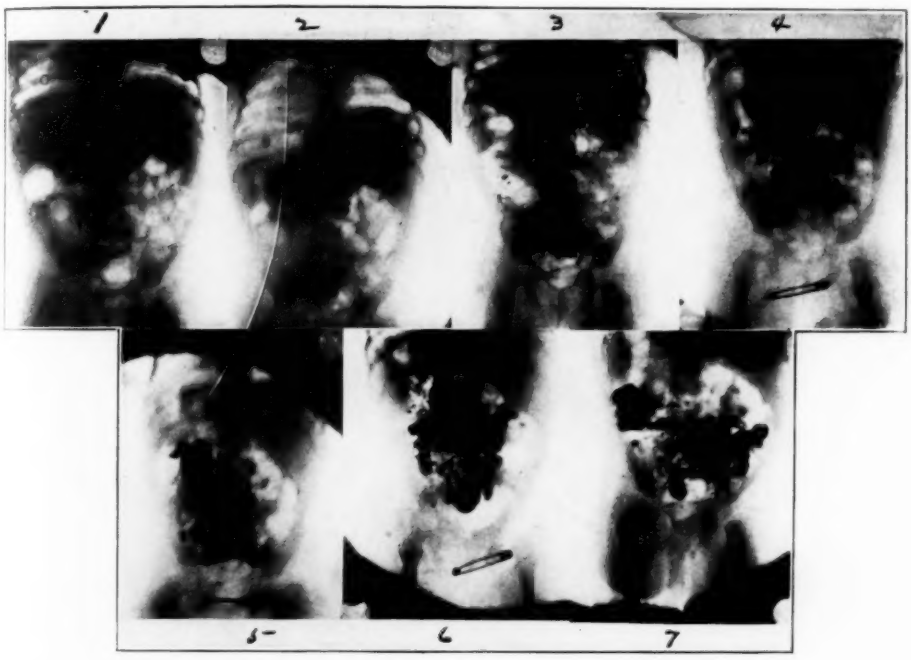

Fig. 8.—Infant Randolph, February 10. See Figure 6.

was taken one hour and twenty minutes after No. 3, and the remaining plates in the series (5 to 8) at thirty-minute intervals. The last plate taken three hours and twenty-minutes after the second feeding shows a considerable amount of bismuth in the stomach. The inference is strong that crowding the feeding produced a condition of stasis, resulting in retention of the gastric contents.

Plate 9 (Plate omitted).—Magee. Aged 16½ months, was given 6½ ounces of its regular feeding with 150 grains of bismuth. The second radiograph shows the stomach contracted down on a considerable residue four hours and ten minutes after the feeding. The third plate is the first of a second series taken three hours after a bismuth feeding, the

residue in the stomach being practically the same in amount as after four hours and ten minutes in the previous feeding. The fourth plate was taken immediately after the regular feeding without bismuth. The residue of the previous feeding has not mixed with the new milk, but has been pushed into the pyloric end of the stomach, and in the last radiograph taken one-half hour later, has to a large extent passed out of the stomach.

Plate 16 (Plate omitted).—Devlin. Aged 1 month, weighing 6 pounds, was given 2 ounces of its regular feeding. The case was one of marked pyloric spasm. At the end of two hours the bismuth was massed

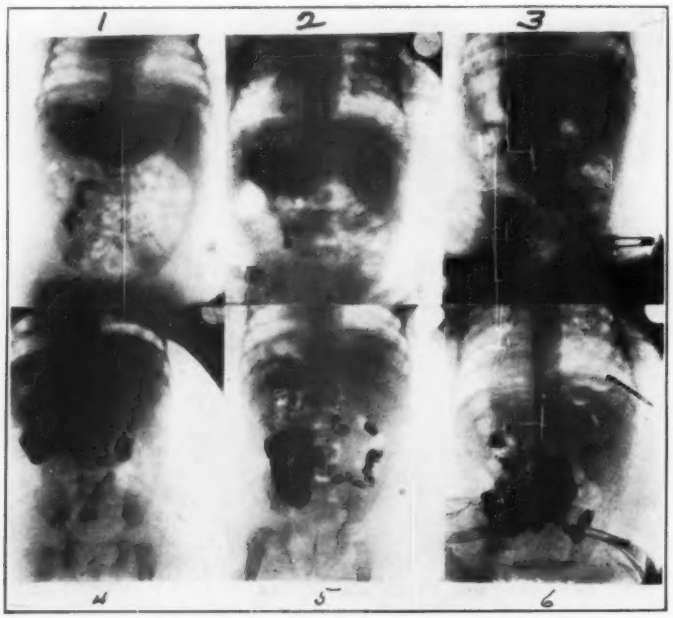

Fig. 9.—Infant Randolph, February 7. See Figure 6.

in a round ball at the pyloric end of the stomach. A second feeding without bismuth was given and the third radiograph taken three and one-half hours after the first bismuth feeding shows but slight change in the appearance of the bismuth residue with only small traces of bismuth in the small intestines. This may possibly have been a case of partial stenosis of the pylorus.

Plate 15 (Plate omitted).—Shea. Aged 2¾ months, weighing 6 pounds, was given 3 ounces of his regular feeding with bismuth. The second photograph taken two hours after the bismuth still shows a large amount of bismuth in the stomach, which in the third plate, taken immediately after another feeding without bismuth, has very largely

disappeared from the stomach. The mechanical action of the new feeding in pushing out the residue of the previous feeding is well shown in this series.

Figure 4.—Gillis (before operation). A case of pyloric stenosis, showing almost complete retention of the stomach contents after a bismuth meal with marked dilatation, only small traces of bismuth appearing in the intestines after two hours. The first radiograph was taken with the stomach empty; the second and third were taken after a bismuth feeding, the child lying on its stomach in No. 2; on its back in No. 3.

Figure 5.—Gillis. (The same case after operation by Dr. Mixter.) The first radiograph was taken with the stomach empty. The second

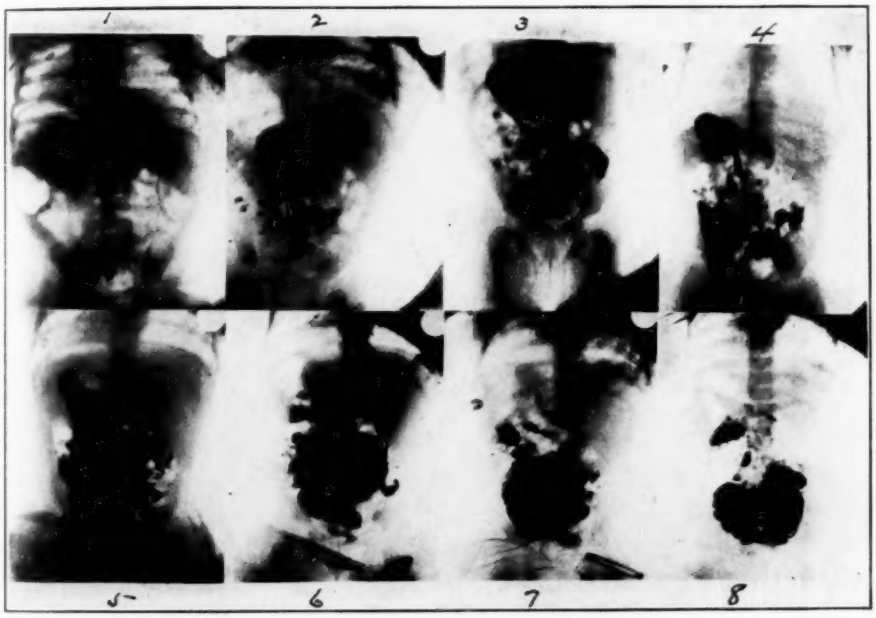

Fig. 10.—Infant Randolph, February 8. See Figure 6.

was taken immediately after an esophageal feeding with bismuth, showing the immediate emptying of a large part of the food. The remaining four radiographs taken at ten minute intervals show the rapid expulsion of the stomach contents, the greater part of the feeding having passed out fifty minutes after the esophageal feeding.

Series of February 1 to February 11 (Figs. 6 to 11, inclusive) represents the first attempt to study systematically the effect of foods of different composition in the same baby. The infant (Randolph) was 6½ months old, breast-fed and was in the hospital for the treatment of seborrhea and eczema of the scalp. The mother nursed the baby several

times a day during the eleven days on which the radiographs were taken, bringing enough milk with her to supply the feedings when she could not nurse the child directly. The breast milk was analyzed and found to consist of:

Fats	2.1
Sugar	6.62
Proteids	1.52
Mineral matter	0.06

The baby took 5 ounces at a feeding. In each case, 1 ounce of the feeding with the bismuth was given by tube and washed down with another ounce of the milk. The remaining 3 ounces were given through

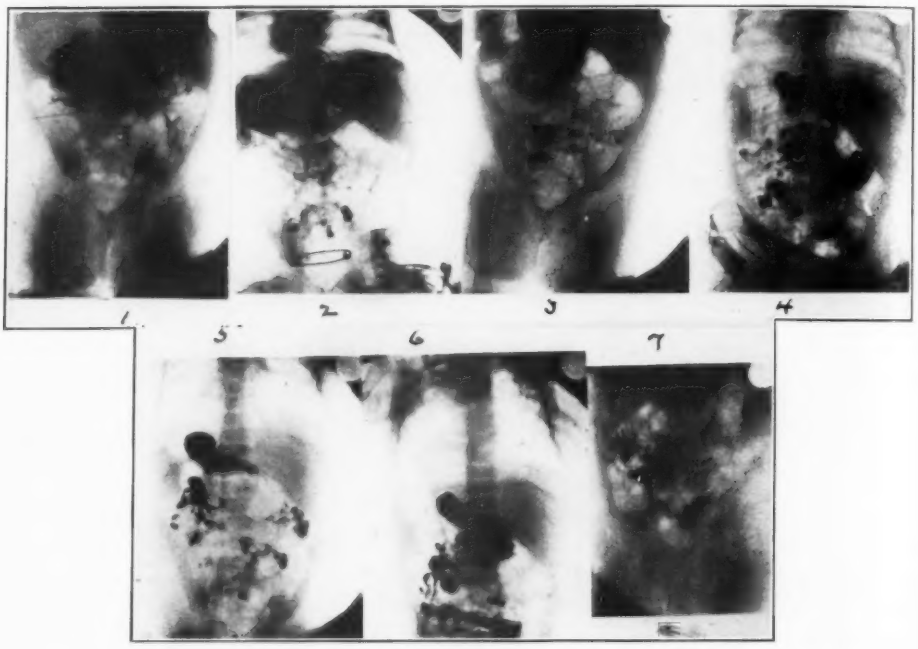

Fig. 11.—Infant Randolph, February 11. See Figure 6 and description in text.

the nipple. The amount of bismuth in the first series was 1½ level teaspoonfuls; in the experiments of the remaining series, two rounded teaspoonfuls.

Series of February 1 (Fig. 6). Five ounces of the breast milk with bismuth were given in the manner described. One-half hour was allowed for the nursing period, after which radiographs were taken at one-hour intervals. The stomach in this case emptied itself practically in two and one-half hours. (No. 3.)

Series of February 3.—The radiographs were unsatisfactory and were repeated on February 5.

Series of February 5 (Fig. 7).—The amount of bismuth was doubled. The baby was given a modified whey-cream mixture, accurately calculated to duplicate as nearly as possible the composition of the breast milk, as shown by analysis; i. e.,

Fat	2.1
Sugar	6.62
Whey proteid	0.90
Casein	0.62

Lime water, 20 per cent. of the milk and cream.

The result showed practically the same emptying time as in the case of the breast milk; i. e., two and one-half hours. (No. 3.)

Series of February 10 (Fig. 8).—A modified milk showing the same sugar and protein percentages with the same amount of lime water in ounces as in the series of February 5 was given. The fats were, however, raised to 4 per cent. The composition of the food was, therefore,

Fat	4.00
Sugar	6.62
Whey proteid	0.90
Casein	0.62

The emptying time of the stomach was four and one-half hours (seen in No. 5); that is, the increase of 2 per cent. in the fat percentages over that of the breast milk and the modified milk of the same composition, resulted in a retention of the contents two hours longer than in the first two series.

Series of February 7 (Fig. 9).—The composition of the food in the series was

Fat	0.00
Sugar	6.62
Whey proteid	0.90
Casein	0.62

That is, the fats were excluded in this instance, the composition otherwise remaining the same. The stomach was nearly empty in four and one-half hours (No. 5); completely so in five and one-half hours (No. 6). Compared with the series of February 5, in which the fat percentage was 2.1, the only difference, the emptying time was from two to three hours longer, but was only slightly longer than when the fat was 4 per cent. In repeating these series in another baby, as I hope to do, it will be interesting to see if this curious phenomenon is seen. The question which naturally suggests itself is: Does the presence of a moderate percentage of fat, such as 2 per cent., in some way stimulate gastric peristalsis? Obviously, one observation on this point does not justify any opinion.

An attempt was then made to show the effect of high percentages of casein; first with 2 per cent. fat, and then with no fat, the sugar percentage remaining the same.

Series of February 8 (Fig. 10).—The composition of the milk on this date was

Fat	2.1
Sugar	6.62
Proteids	3.50

The emptying time of the stomach immediately jumped to six and one-half hours at least (No. 7). A small trace of bismuth remained at that time—scarcely to be considered—and in the next radiograph (No. 8), at seven hours, this had not disappeared. Another radiograph taken at the end of eight hours, and not here reproduced, showed no trace of bismuth. Compared with either breast milk or with a modified milk of the same composition as the breast milk, the increase of protein to 3.5 per cent. delayed the emptying time of the stomach four and one-half, or at the extreme, five and one-half hours.

Series of February 11 (Fig. 11).—The composition of the milk on this date was

Fat	0.00
Sugar	6.62
Casein	3.50

That is, the fats were excluded and the casein raised to the maximum. The result was extremely interesting. Radiograph No. 1 represents the stomach at the end of one and one-half hours. At the end of seven and one-half hours (No. 7) there still remained a considerable residue in the stomach. The experiment was not carried to the complete emptying time, as the baby was obviously greatly in need of food. Still in this case, we see again the possible influence of fat, for in the series of February 8, with the same casein percentage, the stomach was practically empty in six and one-half hours, whereas in the fat-free, maximum casein mixture, it was by no means empty at the end of seven and one-half hours. Further investigations along these lines are now being carried on.

In closing, I wish to record my indebtedness to Drs. Wyman and Percy, house physicians at the Children's Hospital, for their interest and cooperation in the work; and to Mr. Mulvaney, assistant roentgenologist, who has taken all the radiographs here reproduced. I have particularly to thank Dr. Ariel W. George, under whose general direction the technical work has been done, for his many courtesies and helpful suggestions.

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REPORT OF A CASE OF AMYOTONIA CONGENITA (MYATONIA CONGENITA–OPPENHEIM) WITH AUTOPSY *

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As the number of cases of amyotonia congenita reported now totals but some seventy cases, about one-quarter of which are accompanied by autopsy protocols, one need not apologize for adding to the literature on this rare disease. The case I am about to report came to me from the service of Dr. John Lovett Morse, of the Boston Children's Hospital, early in November, 1912. The child had been admitted, *in extremis,* three days before, suffering from an intercurrent attack of bronchopneumonia, so that a very thorough physical examination was impossible. The diagnosis of amyotonia was based on the history of the case and on the report of the Outpatients' Department, where the baby had been previously examined. These reports, supplemented by a special history, kindly supplied me by the family physician, Dr. J. Shohan, by the report of Dr. Fairbanks on the nerve reactions and by the autopsy findings, make the diagnosis perfectly clear.

In the following article I shall give a clinical and pathological report of the case, supplemented by a comparison with those cases already reported.

CASE REPORT

History.—Martin M., aged 3½ months. The history of the parents was negative, except for the following history of parturition: This child was the eighth of Russian Jewish parents. Their first child, born in 1895, with instrumental assistance, was paralyzed from the time of birth. Fetal movements had always been feeble. The baby never cried vigorously, always breathed with difficulty, it never learned to hold up its head nor to sit up, the head falling forward on the chest when unsupported, the chest and knees coming together if the child was placed in a sitting posture and then let go. The mother thinks that the paralysis was left sided, but was uncertain. The baby died of convulsions at 6 months. Two years later a second child was born, also paralyzed at birth. The fetal movements were feeble, as in the first pregnancy; the paralyses were symmetrical and although the child could breathe normally, it could never move its arms above its head, nor could it move its legs. Its fingers were normally used. It died at 9 weeks, of convulsions. During the following twelve years five normal children were born; in each pregnancy fetal motion came on in the fourth month, was strong and vigorous and the children are now all alive and well, excepting the fifth who died at 9 of rheumatic endocarditis.

The past history of Martin M., the eighth child, was as follows: He was born at full term, after an instrumental delivery. The mother had not felt action until after the fifth month; a month later than in the case of her normal pregnancies; at this time motion was very feeble and remained so till the child

* From the Department of Pathology, Harvard Medical School.

was born. It was even feebler than in the case of the first two pregnancies. The mother had marked edema of the lower extremities for the first time in her experience. This child was "limp like a rag" at birth, did not cry until spanked and then only feebly. It never cried lustily. It moved neither arms nor legs, its hands were clenched, it breathed, as its brother put it, "like a cat that wished to vomit." After a few weeks the hands opened out, the child using its fingers fairly well, the diaphragmatic type of respiration became less evident and was superseded by normal breathing up to the time of onset of the bronchopneumonia. *In other words, the early paralysis gave way to definite improvement.* Movement in the arms and legs became progressively better up to a certain time and then stopped. Electrical treatment and massage benefited the child but little.

The present illness dated back to a few days prior to admission, when the baby began to show signs of embarrassed respiration and difficulty in nursing, owing to its inability to nurse and breathe adequately at the same time. It had some fever.

Physical Examination.—The physical examination, compiled from the various reports consulted, is as follows: Well-nourished, well-built child, with a superabundance of subcutaneous fat. Color fair, face slightly flushed on admission, no cyanosis. Cry feeble but clear. Respiration when seen two weeks before at outpatients' department, normal; at time of admission to hospital, grunting and labored. The baby cannot raise its head, nor move its arms at the shoulders; nor can it move the legs at the hips or knees. It flexes its forearms feebly, shows complete extensor paralysis at both wrists. Both thumbs are dislocated outward at the interphalangeal joint. It shows double external paralysis of the feet, though the toes are moved freely. Fingers move well, no facial paralysis. Electrical reaction of the muscles retarded, but no R. D. given. The tendon reflexes are diminished, but not abolished.

The head is well-formed, fontanel small, 2 by 1.5 cm. Mouth shows moderate obstruction of the air-passages by adenoid growths in the nasopharynx, superficial lymph-nodes not enlarged anywhere in the body. The thymus not palpable in the interclavicular notch. Chest bulges slightly on the right, above; in this area bronchial breathing and dulness, as well as behind, almost to lower border of scapula. Heart-sounds clear, no murmurs nor enlargement noted. The abdomen is tympanitic, making wide respiratory excursions. Spleen not felt, liver normal in size. Otherwise negative. White cell count 30,000.

Death on third day after admission.

Necropsy.—The autopsy protocol, slightly abbreviated, follows:

Body: Is that of a large, male, white baby, pale and very fat. Length, 63 cm. The arms and legs are particularly fat and flabby, the former held in the "fin" position, the hands in extreme pronation, the fingers slightly flexed, their backs touching the child's flank. The thumbs are dislocated outward at the interphalangeal joints. The legs lie flaccid and slightly everted. Rigor mortis is absent, livores mortis present to a slight degree in the dependent portions of the body. Head small, well-formed, corresponding with data already given in physical examination. Chest slightly barrel-shaped, abdomen distended and flabby, overhanging the flanks.

Primary Incision: Subcutaneous fat very abundant, one is immediately struck with the unusual pallor of the muscle, which is doughy and flabby to the feel, looking not unlike raw pork. The cut surface has a somewhat gelatinous appearance. Portions of the pectoralis, rectus abdominis, quadriceps extensor femoris, sterno-cleido-mastoid and diaphragm removed for examination. The intestines are distended, the liver presents 2 cm. below the free border of the ribs. Diaphragm at normal level. On opening the thorax, the lungs are found to be dark-reddish in color, lying free, not collapsed, rather voluminous. The heart presents over an earea 3 cm. square. The thymus is large, but not abnormally so. On cutting the diaphragm, it is found to present the only approximately normal-looking muscle as yet encountered.

The heart weighs 25 gm. and shows no abnormalities. The lungs present the usual features of an extensive bronchopneumonia, in this case involving almost entirely the upper and lower lobes of the right lung, which weighs 64 gm. as against 40 gm. for the left. The bronchi show reddening and increased secretion throughout their extent. Among the organs of the neck, the thymus and thyroid were examined with particular care. The former weighs 10 gm., is in no way macroscopically remarkable and shows no thickening or hemorrhagic areas. The thyroid is of homogeneous consistence, in no way remarkable. The muscle of the tongue, pharynx and neck does not seem to be involved in the pathological process; it is red and normal in appearance.

The abdominal organs show nothing of interest, save for a marked local inflammation of the duodenum. The adrenal glands are normal in appearance, the cortex of a somewhat pale, yellowish color, its thickness is in the proper ratio to that of the medulla.

Fig. 1.—Field × 200 diameters, at the top, "large" or normal fibers, in the middle connective tissue described in text as resembling muscle in the arrangement of its fibers. Below, the most numerous, "smaller fibers." Measure the fibers with a millimeter rule. Phosphotungstic acid-hematoxylin.

The brain is large and congested, otherwise shows no gross abnormality, although systematically examined. The same is true of the cord and medulla, which will be considered later.

Diagnosis.—Amyotonia congenita (?); extensive bronchopneumonia of the upper and lower lobes of right lung. Pulmonary congestion. Laryngitis, tracheitis, bronchitis. Acute duodenitis. Cause of death, bronchopneumonia.

Microscopic Examination.—Examination of the pneumonic areas in the lungs shows typical confluent foci of bronchopneumonia, which is distributed as already noted. The thymus, thyroid and adrenal fail to show anything abnormal. The number of Hassall's corpuscles in the former is neither above nor below the normal. There are several areas of new-formed, or forming, corpuscles.

Special Examinations.—We now come to the more important microscopic examinations, namely, those of the muscle, peripheral nerves and central nervous system. In the case of the former, portions of the pectoralis major, diaphragm, rectus abdominis, quadriceps extensor femoris, sterno-cleido-mastoid, tongue and heart, were fixed in formaldehyd solution and Zenker's fluid, and stained by the following methods: Hematoxylin-eosin, Mallory's phosphotungstic-acid hematoxylin-orange G., Weigert-Van Gieson, Bielschowsky, Luden van Heumen modifications of the Weigert medullary-sheath stain, Sudan III and Nile-blue sulphate. The tongue and heart-muscle give the only normal pictures.

On examining the affected muscles, one is immediately struck by the discrepancy in the diameter of the majority of the fibers, most of them being very slender, while others are of normal size and appearance. The normal fasciculi lie scattered through the abnormal portions, the contrast being the greater as they lie in groups embedded in the masses of smaller fibers, and as they are in

Fig. 2.—An area of round-cell infiltration, same magnification as Fig. 1. Large, "smaller" and "small" fibers all well shown. Phosphotungstic acid-hematoxylin.

the minority. The lack of any intermediary fibers to bridge the gap between these two sizes of fiber, adds to the sharp contrasts. These changes in diameter do not apply to the diaphragm, where the fibers are all of normal size and disposition, but of abnormal staining properties. In a few isolated instances, in the case of the skeletal muscles, particularly the rectus abdominis, one can find places where there is a marked cellular infiltration, the cells being of the small round type, with occasionally polymorphonuclear leukocytes among them. Marked invasion of the muscular tissue by fat and connective tissue, with replacement of the muscle fibers by these elements, is not found; here and there are islands of fatty tissue in the most broken-up portions of the muscle, a manifestation of the general adiposity of the subject, I believe, rather than a replacement invasion. It must be borne in mind that the cellular infiltration appears only in very few of the slides examined and does not represent the usual picture. The more

usual type of muscle section is a closely arranged mass of very small fibers, with islands of larger fibers imbedded in them, in the form of long strands or of elliptical masses; the picture is made up almost entirely of muscle tissue, as shown in Figure 1. Figure 2 shows an infiltrated area.

Occasionally one also finds dense strands of connective tissue, the fibers of which are arranged similarly to muscle fibers, stain deeply with acid fuchsin or Orange G., and resemble tendons in their structure, although occurring where tendons are not usually found. They also suggest scar-tissue in muscle previously cut through, or the tendon-like areas in the heart muscle in chronic interstitial myocarditis. One of these bands appears at the center of Figure 1.

Concerning the more minute changes in the muscle, the following facts are noted:

Fibers: Some small, some large, very few transition phases, so that fibers of normal caliber (20-50 microns) lie in close juxtaposition to fibers of very small

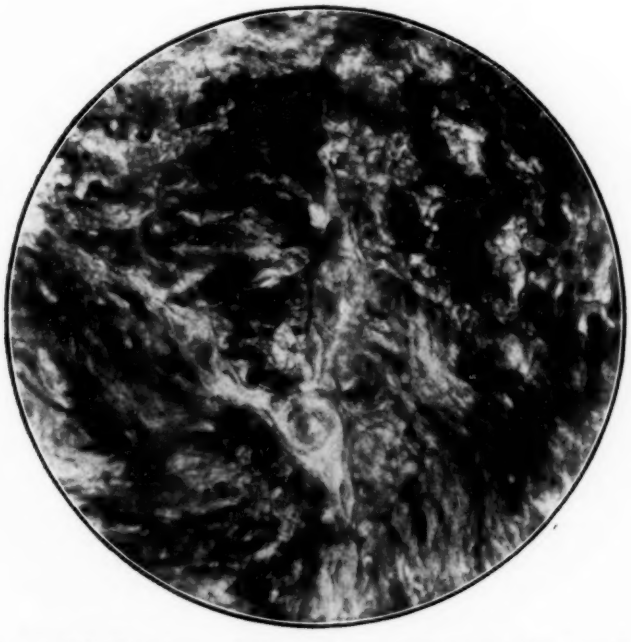

Fig. 3.—× 550 diameters. Section of one of the muscular branches of the femoral nerve, from thigh. The dark rings in upper middle portion of the photograph are normal myelin sheaths, the scarcity of such normal sheaths is easily made out. This nerve one of the average types, others show no myelin whatever. Luden van Heumen stain.

caliber (3-5 microns). The latter, occurring in a similar, yet very different disease, have been aptly termed "*muscles en miniature*" by Hoffmann. Some fibers, still smaller than those already mentioned, are found to consist of merely two or three fibrillae and measure only 1.5 to 2.0 microns; these are not as numerous as the somewhat larger type (henceforth to be termed "smaller fibers"). Besides these, there are fibers that suddenly diminish in diameter, beginning almost normal in caliber and then suddenly dwindling down to a whip-like extremity, like the body and head of the *Trichiuris*. The course of the large fibers is straight, that of the smaller usually so, while the smallest are almost always wavy in their course and somewhat frayed-out in their appearance.

In the case of the larger fibers one can easily find areas where these have undergone a hyaloid change, having a waxy look, with fracture-lines, not unlike the appearance of waxy casts in urinary sediments. This hyaloid change is noted chiefly in the stained sections; in the impregnated (Bielschowsky silver stain) preparations it is replaced by a difference in intensity of the detail, by a pallor in the striae and other structures of the muscle fiber. It may be general or patchy and scattered through an otherwise normal-looking fiber in the form of rounded or ovoid areas. The fact that it appears only in the true stains, while it does not show in the impregnations, suggests that it represents the presence of some hyaloid substance which masks the finer structures of the muscle fiber, rather than an absence of these structures. This is an important point to note. Vacuoles also appear in some of these areas, filled with a granular or hyalin material which stains deep pink with eosin, dirty greenish to olive with Weigart-Van Gieson, and blackish to brownish with the hematox-

Fig. 4.—Section of lower cervical region of cord, showing marked pallor of the pyramidal tracts and the shrunken condition of the anterior horns, also their pallor. Tract of Goll and Burdach unusually prominent by comparison. Luden van Heumen technic.

ylin-lakes of the phosphotungstic acid and Luden van Heumen stains. In some of the hyaloid areas the anisotrophic material of the disks is coagulated to larger or smaller masses, with staining characteristics similar to those of the contents of the vacuoles. These vacuoles do not occur in large numbers in my preparations. The Sudan III and Nile-blue stains show a fatty infiltration of the larger, and in some of the smaller fibers, which is either diffuse, or in the form of bands of fat-droplets arranged at short intervals and not in relation to the cross striations of the fibers. These droplets are composed of neutral fat, staining orange with Sudan and pink with Nile-blue. These stains show a weak affinity for the contents of the vacuoles, which are stained light orange with Sudan, bluish-green with Nile-blue (lipoid reaction).

The degenerative changes in the smaller fibers are similar to those just described in the case of the large ones, but they occur less frequently and less regularly and are easily overlooked, the majority of these fibers presenting perfect striations and staining characteristics (hence "*muscle en Miniature*").

The nuclei of the fibers are, on the whole, of normal appearance, though occasionally, particularly in those areas where there is cellular infiltration, they are vascular and pale, with sharp outline and karyosomes. There are also areas where the nuclei show a certain degree of pyknosis. The number of nuclei is greater in the smaller than in the larger fibers, but as this is normally the case and as there are no areas of contiguous or dividing nuclei (as seen in atrophic lesions), it is best to interpret this statement with some reserve. The nuclei at the fiber extremities are definitely increased in number, often being heaped together in masses; but this is also a normal phenomenon in the growing muscle of young children.

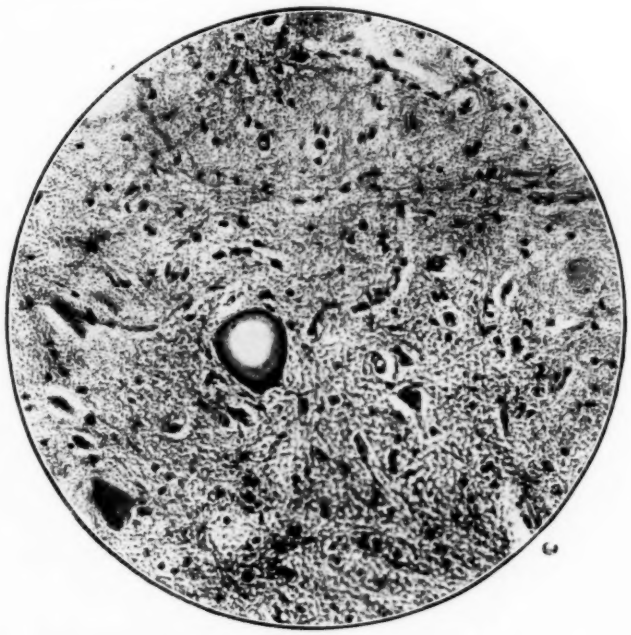

Fig. 5.—Portion of an anterior horn, × 200, showing a cell which has undergone vacuolar degeneration. Notice also marked increase in small round cells and in glia tissues. Phosphotungstic acid-hematoxylin stain.

Fibrillae: For the most part these have a normal appearance both in the large and small fibers; in the former the Krause's lines are darker, somewhat broader and possibly nearer together, in the latter, particularly in the most affected areas, they show an accentuateed lighter area in the neighborhood of the mesophragm, making them appear paired. The finer structures of these disks are in places clearly visible, if one choose thin portions of the sections, the mesophragmata with the "J"- and "G"-granules are demonstrable with either the phosphotungstic acid hematoxylin or Bielschowsky stains. Some of the larger hyaloid fibers have only a few visible fibrillae, one or two, at their periphery; or scattered through their waxy sacroplasm in groups of twos and threes. Sometimes also, one finds isolated sarcous elements lying in the substance of such hyaloid fibers, singly, or in groups. These are often more or less swollen or coagulated in appearance, occurring oftenest in very short, more or less spindle-

shaped fibers (24 by 40 microns in size) having the appearance of embryonal muscles-cells. Such structures are relatively scarce.

Connective Tissue: The connective-tissue elements are, as a rule, not markedly increased, as shown in the preparations of Van Gieson and Mallory phosphotungstic-hematoxylin. In the infiltrated areas and in the pectoralis major are thickened areas like tendons (*vide supra*) as well as the younger, more reticulated tissue. The sarcolemma does not seem to be markedly increased in amount, though there are focal evidences of slight thickening.

Muscle Spindles: Appear to be in every way normal and not unduly numerous, they are not difficult to find and are composed of apparently normal muscle fibers enclosed in sheaths of connective tissue resembling the perimysium. The Bielschowsky stain shows slender, branching nerve-terminals in these organs.

Diaphragm: Though this muscle showed none of the typical lesions of amyotonia, there were, however, areas of great irregularity in staining quality,

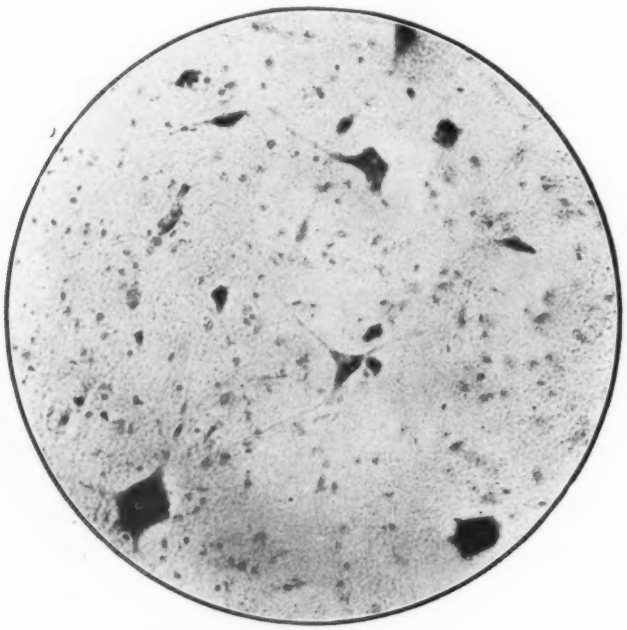

Fig. 6.—× 200. Portion of an anterior horn. Below at left, a normal cell for comparison; above, several shrunken cells, also several arrow-head cells. Carbol-thionin.

where the striae were faint or apparently lacking in the case of the stains. The impregnation method of Bielschowsky showed some irregularity in the intensity of the striae; in some places they seemed run together and obscured by some deposit in the fiber. That these irregularities in staining properties have anything to do with the disease, is not proved; as they were present and marked, I mention them for the sake of completeness.

Peripheral Nerves: The peripheral nerves, which we may best consider under this part of the discussion, show a marked decrease in their medullary sheaths, when stained by the Luden-Van Heuman method, sometimes only one or two fibers having this sheath, usually less than half showing normal myelinization. This will be evident from Figure 3. There is no alteration in the myelinated fibrils; no varicosities or thickenings of the sheath are to be found. In all the peripheral nerves examined in the muscles already listed as excised for exam-

ination, this condition obtains and the smaller branches of the nerves are, for the greater part, invisible, owing to their lack in myelin-sheaths. Even the Bielschowsky impregnation-method fails to bring out a normal number of nerve terminals; those which do stain are distributed to the larger fibers and although not very complex in their ramifications, seem to be normal. The smaller fibers seem to be without innervation, no terminals could be demonstrated in their case. The larger trunks of the peripheral nerves show changes somewhat similar to, and in accordance with, the changes noted in the muscle and in the central nervous system (q. v.). The fibers show a diversity of caliber, in many ways resembling that in the muscle, and are either small and thin, or swollen and vacuolated and somewhat varicose, with a netted appearance. Incidentally, the silver impregnation here used served for the description of that method under the head of muscle changes; it was only applicable to the rectus abdominis, as the rest of the muscles had been embedded in celloidin or paraffin and could not be used for impregnation.

Central Nervous System: Examination of the nervous system was as thorough as the material permitted. Owing to objections on the part of the family, the whole cord could not be removed; by drawing out the cervical portion as far as possible through the foramen magnum, I was able to cut it off well down near the level of the upper thoracic region. In this way the nerve roots were unfortunately sacrificed as they were pulled off. The cerebellum, together with the higher levels of the medulla, were unfortunaately mislaid; the entire Rolandic area was obtained. The material was fixed in Zenker's fluid, excepting for the brain, which was fixed in 10 per cent. formol.

The nerve tissue was stained with hematoxylin-eosin, Weigert iron-hematoxylin-eosin, the Weigert-Van Gieson stain, the Mallory phosphotungstic acid-hematoxylin stain, carbol-thionin, nigrosin, Luden van Heumen's modification of the Weigert medullary sheath stain and, in the case of the brain, with the Bielschowsky silver method. These were fairly successful in supplementing one another, so that a very good idea of the existing lesions could be obtained. The Luden van Heumen method deserves special mention here as a new, reliable, and in my experience thoroughly trustworthy substitute for the more lengthy and difficult Weigert or Pal methods, requiring only about an hour to run through and giving brilliant, clear pictures in every instance.

The lower cervical region shows the following lesions: In the gray matter the anterior horn is the seat of pathologic changes; the cells are reduced in number, most of them in size and some of them show vacuolar degeneration and "acute swelling." These changes are more marked in the cervical region and will be fully described when I come to it. The fibers in these horns are pale, scattered and the horns as a whole, noticeably shrunken in size. The exits of the nerves to the anterior roots are pale and indistinct, the white matter shows pallor of all the tracts except those of Goll and Burdach and the direct cerebellar, the former standing out like a black wedge between the posterior horns, the contrast between its color and that of the other tracts being very marked. The tracts of Gower and Deiter show some pallor; the lateral and anterior pyramidal tracts are markedly pale, the pallor being due to a diminution in the number of myelinated axones. Figure 4 shows this condition very well.

The upper cervical region shows much more marked lesions of the gray matter, somewhat less marked tract degenerations or pallor. The normal anterior horn cells are markedly decreased in numbers, in thirty-eight slides there was an average of from three to eight normal cells to a horn. In some cases the Nissl bodies are thick, clumped at the periphery of the cell and very deeply stained. This is naturally most evident in the carbol-thionin preparations. Occasionally one finds large, swollen cells, with a large vacuole at the usual site of the nucleus, the latter being crowded off to one side, or broken up, the Nissl granules disintegrated and clumped in a granular mass at the periphery. (Fig. 5.) The most interesting condition, however, is the presence of many small cells resembling the posterior horn cells in size and shape. Roughly

triangular, like arrow-heads, sometimes very much elongated, with pale Nissl granules, small nuclei and nucleoli. Other cells are merely small counterparts of the normal anterior horn cell. The measurements of these three types are as follows:

Large Cells: 28 to 40 microns in diameter, nucleus 10 to 17 microns, nucleolus 3.5 to 5.0 microns.

Small Cells: Diameter averages 17 microns, nucleus 10 microns, nucleolus 2.0 to 3.0 microns.

Triangular Cells: Average 24 by 8 microns; largest 50 by 9, smallest 12 by 7 microns.

The cells of the posterior horns show no change; there are many cells in the dorsolateral horn which resemble the smaller type seen in the anterior horns in this case. There is an increase in small round cells and in glia fibers in the anterior horns, while the myelin-sheath stain shows a pallor of this region and a marked lack of definition in the axones which emerge to form the anterior nerve roots. This pallor is more marked in the mesial axones than in the laterally placed fibers, some of the former being represented by light brown streaks. To sum up, the picture with the Luden van Heuman stain is exactly the reverse of that with the phosphotungstic acid-hematoxylin; in the former the anterior and lateral portions of the cord are paler than the posterior, whereas in the latter they are darker, owing to the gliosis present. The lack of myelin seems to be made up for by an excess in glia tissue. The tracts of the white matter show the same changes as already described in the case of the thoracic segments, pallor of the columns of Gower, Deiter and the pyramidal tracts, particularly the anterior. The direct cerebellar tract is usually apparently unaffected, though in places, lower down (as in Fig. 4) it is patchy.

Sections from the higher levels of the cord correspond to those in the cervical and thoracic segments examined. The pallor of the tracts already enumerated is evident as high as the olive, which was as high as I could examine them. The cells of the anterior portion of the formatio reticularis of the medulla show changes analogous to those of the cells of the anterior horns at lower levels. The decussation of the pyramids shows a slight pallor, hard to recognize owing to the normally broken-up condition of the tract at this point; higher up, however, before the decussation and where the pyramids are more compact, one can easily make out this pallor.

At the level of the olivary nuclei the pathologic lesions are less evident than they are in the lower levels, but nevertheless present. The large cells of the substantia reticularis grisea show the same vacuolar degeneration as do the cells of the anterior horns and the formatio reticularis, though the presence of smaller cells of the triangular type is less marked. The same tracts are involved as in the case of the other regions described. The external arcuate fibers and the tractus spinalis trigeminus are of a deep black, and uninvolved. No changes could be found in the cells of the nuclei of the cranial nerves. Between this level and the Rolandic area, no examinations could be made. In the cortex cerebri no changes can be ascertained; the various layers of cells, the white matter, and the neuroglia all seem to be in good condition.

DISCUSSION OF THE CASE

Since Oppenheim first described this disease in 1900, nearly seventy-five cases have been reported, about thirteen of them accompanied by autopsy findings. It will be seen, therefore, that the disease is gradually being placed on a sound footing among the myopathies, as we are now able to compare a fairly large number of cases and to judge what symptoms and lesions are the most frequent and constant in their occurrence. I shall not attempt to give a description of the disease, rather referring

the reader either to Oppenheim's article in his *"Lehrbuch der Nervenkrankheiten,"* Edition 5, 1909, to Cassierer's article in Springer's *"Handbuch der Neurologie,"* 1911, II, or to one of the numerous articles on the subject to be found cited in the bibliography at the end of this paper. The most recent and best-written are those of Archangelsky, Councilman, Griffith and Griffith and Spiller, and very excellent discussions by Marburg and Thorspecken.

My reasons for making a definite diagnosis of amyotonia congenita in this case will be evident if we take up the clinical and pathological features point by point. Before doing so, however, I wish to add to those of Griffith, Concetti, *et al.*, my plea for the adoption of the term "Amyotonia Congenita" rather than the original "Myatonia Congenita," which is a clumsy combination of abbreviated stems and one too liable to be misspelt "Myotonia," which is the name given Thomsen's disease, an entirely different state of affairs from that under discussion.

Considering the family history of Martin M., we have, first of all, two similar cases in the family, both of which were very suggestive of the same disease, but in which the diagnosis cannot, of course, be definitely made. The disease was, in this case, probably familial; a characteristic rather more common in the Werdnigg-Hoffmann type of infantile progressive muscular atrophy. The literature, however, is not lacking in familial cases of amyotonia. Marburg considers it a possibility. Concetti reports a case which was also one of two children affected in the same family, and cites Sorgente's report. He considers it rare, but quite possible.

To quote Marburg, we can differentiate the Werdnigg-Hoffmann syndrome and amyotonia as follows:

Amyotonia Congenita	*Werdnigg-Hoffmann.*
Congenital.	Acquired early in life.
Usually single, rarely familial.	Usual familial.
Generalized hypotonia.	Localized atrophies, beginning in pelvic region and spreading.
Atrophy masked, not grossly apparent.	Atrophy easily recognized and apparent.
Tendon reflexes absent.	Proportional to the atrophies.
Stimulated by electricity or the hypotonic reaction given. (Farad. 0, Galv. +)	Reaction of degeneration. (R. D.)
Course with improvement.	Progressively worse, a mere skeleton at 4 to 5 years.

The concensus of opinion is that in amyotonia the fetal motion in utero is markedly weak, appearing later than normal. Archangelsky, Concetti, Marburg, Schippers and many others. (See Councilman's résumés or Griffith's.) My case was definitely of this type, as were the two first children in the family. In most cases the child has been born limp and paralyzed. (Archangelsky, Councilman, Schippers; see also

résumés, Ashby, Ausset, Baudouin, Berti, Bing, Cattaneo, Coombs, Collier and Wilson, Collier and Holmes, Iovane, Tobler, Rosenberg, etc.). There are, however, many cases in which the paralysis has come on during the first month or two after birth. In Councilman's case the child "hung down like so many skeins of yarn" at birth. A consideration of my case, as well as of the history of child's two sisters, will clearly show that it was congenital, if not definitely prenatal.

The type of paralysis in this case was of the generalized, hypotonic type, not localized, nor starting in the pelvic region and it showed definite improvement up to a certain point. The child's hands, extremities and accessory breathing muscles had been totally paralyzed at birth; but they slowly improved in their functional capacity in the first few months. This speaks for amyotonia and against the Werdnigg-Hoffmann syndrome. Another point in the differential diagnosis is the absence of *gross* atrophy; outwardly the child's body gave no evidence of atrophy or paralysis, other than the position of the extremities and the thumbs. The absence of the reaction of degeneration and the retarded electrical reactions speak for amyotonia. The diminution, rather than loss of tendon reflexes is somewhat atypical.

If we take into consideration the pathological findings we will see that all the cardinal lesions of amyotonia congenita are present. Grossly, the general obesity, the "fin" position of the arms, the flaccidity of the legs are all typical. That the child had a barrel-chest, rather than the pectus carinatus, usually cited as typical, is an exception. In the general autopsy findings one finds several points of interest; the presence of extensive bronchopneumonia (which is the usual cause of death in this disease and explained by inadequate respiratory functions) and the absence of any lesions in the thymus, thyroid, or adrenal glands. The thymus has been reported as sclerosed, or the Hassall's corpuscles unduly numerous or scanty (Archangelsky, Griffith, *et. al.*). The most recent observations, however, seem to show that in these cases the changes were merely coincident, rather than causative in their nature. The brain, in my case, was large, otherwise showing no gross lesion, which tallies with the findings of Griffith and Archangelsky.

As far as the muscle itself is concerned, the changes described in this case are those already accepted as the type, with the exception of one or two points for which I can find no parallel in the literature. The diameter of the fibers corresponds closely with the measurements of Archangelsky (small, 2 to 4 microns; large, 18 to 20 microns), Councilman (small, 1.5 to 5.0 microns; large, 8 to 35 microns) and Mensi (small, 5.0 to 6.0 microns; large, not stated); mine measuring, small, 2.0 to 5.0 microns; large average, 17 microns. The degenerative changes in the muscle have been described by Councilman and Marburg, the

former's description conforming most closely to my findings (as did his preparations, kindly placed at my disposal). There was more vacuolization in the fibers of his case, and a more even alternation of large and small fibers through the microscopic field, this alternation being in terms of fibers, rather than in terms of fiber bundles or fasciculi, as in my case. He mentions fatty infiltration of the larger fibers only, not stating the type of the fatty substance; in my case the striped type of infiltration, the fact that the substance is definitely neutral fat, and the fact that it occurs to a very slight extent in the smaller fibers are new to the literature. The findings in the peripheral nerves and muscle spindles correspond to most of those on record; as do those on the nerve-endings.

When we come to the nervous system, we again find that most of my observations are in accordance with what has already been observed, although many competent observers report no changes in cord or brain; in two cases reported by Baudouin, one showed these changes, the other did not. (See Griffith.) Councilman's case was also negative as to nerve lesions in the central system. My findings are most closely paralleled by those of Archangelsky and Marburg, to a lesser degree by Mensi; a comparison of the microphotographs and drawings from these four cases will reveal a striking similarity. The diminution in the number of normal cells in the anterior horn is mentioned by all four of us, the presence of "acute swelling" and vacuolar degeneration was mentioned particularly by Marburg and myself. The diameters of these cells are stated by Archangelsky as normally being 30 to 50 microns at five months; in his case they measured 15 to 25 microns, in Mensi's 22 to 39 in children much younger than those reported by Archangelsky and myself. If we lump together all the cells of the anterior horn, large, small and arrow-head or pyramidal types, my figures vary from a long diameter of 17 microns in the smaller cells to 40 microns in the approximately normal survivors. There is mention in one case (Bothmann, see Griffith) of changes in the hypoglossal nucleus, but otherwise I find no mention of lesions of the cells of the anterior portions of the formatio reticularis and substantia reticularis grisea as described in my case. The hypoglossal nucleus was intact in this case, as would be expected from the history and from the normal tongue muscle.

The changes in the tracts of the white matter of the cord and medulla, the shinkage and pallor of the anterior horns of the gray matter, as well as the changes in their roots, are all mentioned in frequent instances. Marburg mentions the gliosis I have referred to and interprets it as a post-inflammatory change.

The following lesions, described in this paper, are as yet without analogy in the literature, so far as I could ascertain:

1. Changes in the diaphragm.

2. True, neutral fatty infiltration of the muscle.

3. Degenerative changes in the cells of the formatia reticularis and substantia reticularis.

CONCLUSIONS

In closing, I shall not attempt to advance any new theories as to the cause or nature of this disease, merely putting myself on record as a believer in the theory that it is a disease rather than a pure arrestation in development. It cannot be gainsaid that there are many points in favor of the latter theory; the presence of the small atypical cells in the anterior horns, of neurons whose sheaths are markedly lacking in myelin, of somewhat rudimentary nerve-endings and decidedly rudimentary muscle fibers ("embryonoid type"), all speak for an arrest in nervous and muscular development. They could also be interpreted as the *results of disease on development*, with consequent retardation of the same, to my mind a much more feasible argument. In support of this we have clearly marked degeneration in the larger cells of the anterior horns, of a nature usually consequent to, or associated with, axonal degeneration. In the case of the muscle one sees definite degeneration in the fibers, definite foci of cellular infiltration and degenerative (?) fatty infiltration; all pointing toward some reaction to disease, rather than to mere inhibition in development. That this disease is a fetal poliomyelitis, as suggested by Marburg and Bernhardt, is borne out by the facts they give in support of their argument; the affection of the anterior horns, the contractures in the muscles, the gliosis, and less forcibly, by the fact of one of Marburg's cases occurring during an epidemic of poliomyelitis in Vienna. But how can we explain the perfect symmetry of the lesions and the clinical pictures, the total lack of unilateral cases in the literature? That the elder sister of my patient was said to be paralyzed on one side is open to doubt, as the mother was very uncertain on this point; it is also far from clear that this was a case of amyotonia. Thorspecken, in his very recent discussion of this disease, takes issue with Marburg on these very points, giving the following reasons for excluding poliomyelitis from the discussion: First, the great extent and symmetry of the paralysis; second, not one muscle shows complete degeneration or absence of function; third, the electrical reactions differ; fourth, there are no vasomotor or trophic changes in amyotonia congenita, nor does the bone-atrophy found in both diseases correspond. (He gives very interesting radiographs of a case of amyotonia.) Fifth, his case was still recovering after having suffered five years with the disease; there was no complete destruction of nerve-muscle function as in poliomyelyitis.

All this leads us no nearer the truth, to be sure; the exact nature of the disease is still to be determined, its cause is still a matter for specu-

lation and the extreme rarity of the affection is very unfavorable for extended research of a clinical or pathological nature. Few observers see more than two or three cases, one or two have reported as many as five or seven, which shows the scarcity of "series" of cases. The whole matter is, therefore, to say the least, not particularly encouraging; perhaps the post-mortem examination of some fetus will, in time, afford us a picture of the disease in its florid, active stage. Till then we must, as I have said, speculate on the findings in cases which I believe, with Marburg, to be the evidence of past disease, now merely the manifestation of the reparative reaction of the body, particularly the nervous and muscular systems, to a morbid process experienced *in utero*.

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A CASE OF CONGENITAL MYXOMA OF THE FEET

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The myxoma is the least frequent among the connective-tissue tumors. It develops in the organs in which it was originally embryonic mucous tissue, but presents itself seldom unmixed. Lustig and Galeotti[1] said:

> Lues ta specie di mixoma che ricorda per la sua struttura il tessuto connettivo embriona le e il tessuto mucoso del cordono ombilicale é molto rara.

Usually it presents itself associated with the other connective-tissue tumors, as fibroma and lipoma. There are then mixed tumors—fibromyxomas and myxolipomas. The myxomas are essentially benign, but, if associated with sarcoma, they acquire the peculiar malignity of that tumor. Certain characteristics are essential to distinguish the myxoma from other connective-tissue tumors. Its edematous consistence, its mucoid appearance on cutting, its bluish-white or yellowish-white color are typical. It consists of granulous spindle-shaped or star-like cells with long, fine processes, which branch off irregularly and intermingle. The cells have generally each a single nucleus; sometimes many nuclei, and show themselves as giant cells. The fixing reagents give to the mucous intercellular substance a granular, finely fibrillar appearance. This mucous substance is metachromatic to thionin stain.

The tumor, generally with regular outlines, is oval-shaped or more or less flat, but sometimes it shows irregular outlines. The myxoma is sometimes vascular, and at other times it shows no vessels at all; it seldom presents elastic tissue. Lorne reports a case of a heart myxoma and Kollmann of a hyaline myxoma, both tumors showing elastic tissue. The myxoma seldom metastasizes. Arterial embolism from myxoma into several organs (kidneys, lungs, spleen and brain) has been reported by Virchow, Berthenon, Robin and Marchand.

In order to explain the pathogeny of myxoma, there are two theories. One maintains that the myxoma originates from the degeneration of lax or fatty tissues which return to their embryonal stage. This theory is supported by Kickefel,[2] who has noted the progressive change of the embryonic mucous tissue into fatty tissue, in four to six months' fetuses.

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1. Lustig and Galeotti: Patologia generale, 1912.
2. Kickefel: Zur Histologie und zur systematischen Stellung der schleimigen oder gallertigen Gewebe der Menschen. Virchows Arch. f. path. Anat., 1892, cxxix.

He believes the myxoma to proceed from fatty tissue returned to the embryonic state (*status mucosus*), but he distinguishes the status mucosus of embryonic fatty tissue from status mucosus of senile fatty tissue and from lipomyxoma. The other school believes myxoma to be the development of a connective-tissue nucleus which has maintained its embryonic state. This theory is to-day generally accepted and is the theory recently supported by Ribbert.[3] Ribbert calls attention to the distinction of myxoma from edematous tumors which by their aspect approach myxoma. They differ because their cell processes are not intermingled and the intercellular substance never shows fibrils.

Jacobsthal[4] considers two forms of myxoma: one, reported by Orth,[5] is an edematous tumor which shows no mucin and presents itself as a

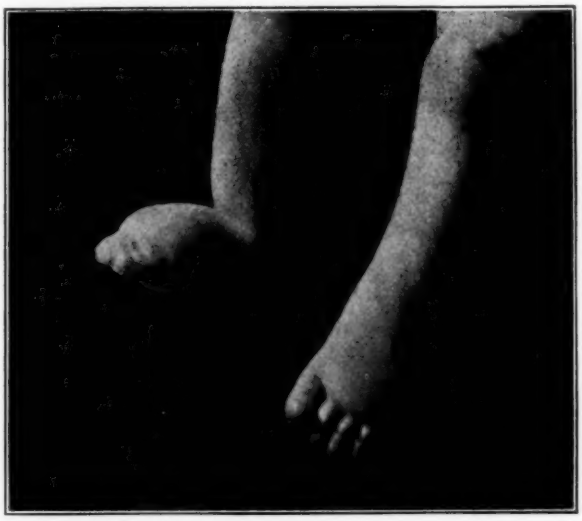

Fig. 1.—Myxoma of both feet in an infant.

sui generis tumor; the second, reported by Koester as being a change of lax tissues into mucous tissue, shows in the intercellular substance many fibrils containing mucin.

The myxoma is often a congenital tumor. Ribbert reports a case of a congenital myxoma of the foot which later involved the fatty tissue of the leg up to the knee. Nové-Josserand reports a case of congenital myxoma in the tibia. Borst's case of an omentum myxoma in a child, aged 9 months, is believed to be congenital. Winsgradow mentions a case of a congenital myxoma of the thymus in a boy, aged 12 months. Mixed

3. Ribbert: Geschwülstelehren.

4. Jacobsthal: Primares Fibromyxom des linken Vorhofes. Virchows Arch. f. path. Anat., 1900, clix.

5. Orth: Ueber Schkim und Schkimgeschwülste, 1895.

myxomas are also often congenital, as the case reported by Nahn of a congenital myxosarcoma in the cheek.

The size of the reported myxomas varies from a minimum of 10 to 15 mm. to the size reported by Kaufmann (16.6 cm.).

Any region which shows embryonic mucous tissue may become a myxoma seat. The favorite locations are the subcutaneous cellular tissue and the navel of the new-born; three cases of the latter are reported by Weber, and Kaufmann publishes a case of *telangiectasic* navel myxoma 16 cm. long and 6 cm. deep.

Waldeyer reports a case of an ejaculatory duct myxoma. Ribbert reports a case of multiple myxoma of peripheral nerves which may be regarded as a case of Recklinghausen's disease.

The central nervous system is also sometimes a myxoma seat. Sancercaux, Virchow, Birch and Hirschfeld report cases of meninges myxomas, and Herz has seen a myxoma in the lateral ventricles of the brain.

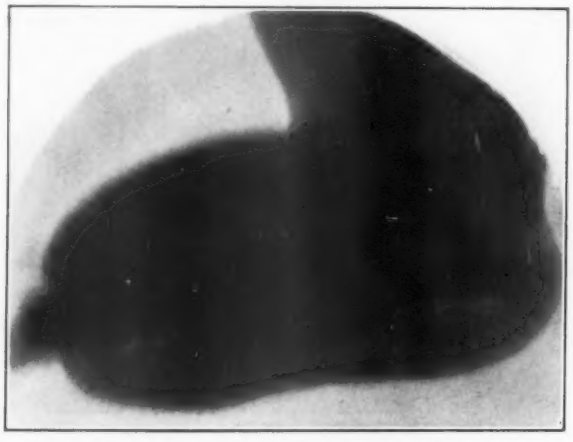

Fig. 2.—Radiograph of myxomatous foot showing the relation of the tumor to the normal structures.

The eyelid myxomas are sometimes mixed with sarcoma. Saltles, Adamuck, Braunschweig and Salzmann report cases of myxosarcomas in the eyelids.

Myxomas often develop on heart valves. Jacobsthal[4] publishes statistics of twenty-one cases of primitive heart myxomas. He excludes three of these cases: the Curtis case as being a single mucous degeneration of the mitral valve; the Wiegandt case (a myxosarcoma) and Jäger's case (a single thrombus). The other eighteen cases, to which he adds his own, were located eleven times in the left auricle; four times on the tricuspid valve[6]; once on the pulmonary valve (Ribbert, 1897);

6. Guth: Ueber einen Fall von papillären Myxoma auf der Valvula tricuspidalis cordis. Präg. med. Wchnschr., 1898.

Fig. 3.—Microscopic section of a portion of myxoma of right foot: A, skin; B, sweat glands; C, subcutaneous cellular tissue; D, "flax" myxoma.

once on the endocardium of the left ventricle (Martinotte, 1886); once in the right ventricle and the other at the heart apex (both cases, Czapeck, 1891). The first reported instance of heart myxoma in children is Jacobsthal's case of a fibromyxoma on the mitral valve. It showed a red-bluish color, was about the size of a hen's egg (6 by 3 by 3 cm.), and was found in a girl aged 4 years, who died with a clinical diagnosis of mitral insufficiency.

As we find in the literature no reference to symmetrical occurrence in myxoma, we believe this present case well worth reporting.

CASE REPORT

History.—A. G., a boy, aged 11 months, was admitted to the hospital Nov. 18, 1911. He was a full-term child; the health of the mother during pregnancy was good; the labor was normal. There is nothing of importance in the family history. At birth the mother had observed that the child's feet were misshapen and showed on the dorsum two symmetrical tumors about the size of a hen's egg, as two little pillows. These tumors developed little by little, causing no disturbance in the child's health. He had no illness from birth to the time of this report and is breast-fed.

Examination.—He is a normal, well-nourished infant, weighs 8,500 gm. and is 66 cm. long. The digestive, circulatory and respiratory apparatus are normal; nothing unusual in the nervous or muscular systems. On the back of each foot one notices a swelling more marked on right foot (Fig. 1). The tumors are elastic and of a hard, edematous consistency. They are compressible, but return to their former shape when the pressure is removed. They are not movable. The measurements of the feet and of the limbs are as follows:

Length of thighs: Right, 28 cm.; left, 28 cm.
Length of legs: Right, 16 cm.; left, 16 cm.

	Right Foot.	Left Foot.
Length	130 mm.	130 mm.
Thickness	43 mm.	40 mm.
Bimaleolar distance	170 mm.	42 mm.
Tarsian level	170 mm.	165 mm.

In order to see if there was a possible adherence of the tumor to bones, we made a radiogram which showed plainly no such adhesion (Fig. 2).

Treatment.—The surgeon to the Children's Hospital, Dr. Leas de Aquino, did an arthroplastic operation. He removed a wedge of skin, subcutaneous cellular tissue and the tumor. From this operation the patient made an uneventful recovery but the arthroplasty was not a brilliant success.

Pathologic Findings.—The pathologic findings in the piece removed at operation were as follows: On section, the tumor was bluish-white, of soft consistency, permitting us to exclude lipoma, a clinical suggestion before surgical intervention.

We employed as fixatives formaldehyd and Flemming's fluid. The pieces fixed in Flemming's fluid in order to examine for fatty tissues, showed that the tumor was not a lipoma. The pieces fixed in formaldehyd were embedded in paraffin, and sections stained with thionin, van Gieson's stain and eosin-hemalum. The sections stained with thionin showed the Hoyer's and Kantorowicz's typical metachromatic reaction. All sections below the subcutaneous condensed cellular tissue showed the tumor tissue *far more flax-like*, showing spindle-shaped and star-like cells with long processes (Fig. 3).

Diagnosis.—The histologic diagnosis is, then, ***primary congenital myxoma of the feet.***

SUMMARY

We again call attention to our case which we believe well worth reporting because (a) it is an unmixed myxoma, a very uncommon occurrence; (b) it is symmetrical, located on both feet with similar appearances. "Symmetry" of this condition thus reported for the first time may possibly help to throw a light on the pathogeny of myxoma.

I wish here to express my indebtedness and my thanks to Dr. Ed. Marques for his courtesy in studying the tumor sections and in confirming our diagnosis.

THE VACCINE TREATMENT OF WHOOPING-COUGH

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The organism of whooping-cough has long been sought and many investigators have described it as an influenza-like bacterium. Notable among these workers was Spengler,[1] who in 1897, called attention to the organism so often found in pertussis sputum. Bordet[2] of Brussels has described at length his work with the bacillus of whooping-cough which he discovered in 1905.

It appears that the organism grows by choice low in the lung and rarely above the larynx. During the early stage of the disease it is found abundantly, but becomes more scanty as the disease progresses. Its culture artificially is slow and difficult, unless the tube is inoculated without other organisms. On account of its slow growth it is easily overgrown by pneumococci and influenza bacilli. The best medium according to Bordet is defibrinated blood, human or rabbit, mixed with an equal quantity of 3 per cent. agar, containing a little extract of potato or glycerin. Culturally on the above medium, in two to four days, it shows a fairly thick, whitish streak, the subjacent blood being hemolyzed but not blackened. This appearance is unlike that of bacteria morphologically similar, such as that of influenza. The organism grows, too, on serum-agar and in liquid media, such as serum-bouillon and blood-bouillon, provided shallow vessels be used so as to provide a large surface in contact with air, the bacterium being an obligatory aerobe.

Under the microscope, according to Bordet, the organism appears as a small cocco-bacillus, in size and shape comparable to the bacillus of influenza. Examined in original cultures, it is usually rather longer and plumper, but during the progress of subcultivation it becomes smaller until it finally appears as a mere point even under the highest powers. Bordet's bacillus is non-motile, negative to Gram, and stains feebly with the usual basic dyes, such as methylene or toluidin blue, but best by weak fuschin.

From Bordet's paper the following is extracted:

The ordinary laboratory animals seem to be but little if at all affected by the infection of this bacteria. An exception must be made in the case of monkeys. Klimenko and Fraenkel claim to have produced a

1. Spengler: Deutsch. med. Wchnschr., 1897, xxiii, 830.
2. Bordet: Brit. Med. Jour., 1909, ii, 1062.

real whooping-cough in these animals. In the rabbit and guinea-pig the bacillus is unable to invade the organism, when injected into skin or peritoneum. When, however, these animals are given a few milligrams of culture from solid media, in the peritoneum, they die with all the symptoms of profound toxemia without the development of a real infection. We may, therefore, conclude that the bacterium of whooping-cough is endowed with toxin-producing properties of a high order. By making use of the method introduced by Besredka we have, in fact, succeeded in extracting an endotoxin, a poison in the guise of a slightly opalescent liquid. In small doses, which represent only a most minute quantity of microbic matter, a fatal result ensues on its injection into a guinea-pig's peritoneum, with the production of the same hemorrhagic and exudative lesions which follow the injection of the living germ. Inoculated under the skin in the dose of 0.25 centigrams it induces a hemorrhagic edema followed by wide-spread necrosis, the skin becoming black, and on the separation of the slough it leaves a vast ulcer of several square centimeters. An analogous necrosing influence has been seen clearly on the surface of the bronchi in affected children. Bordet, on account of these experiments, concludes that the cough in pertussis is due to the liberation of this toxin on the mucosa of the deeper respiratory tract.

The agglutination reaction is observed in using the serum of a pertussis patient. The highest dilution producing complete agglutination was 1 to 60. This is significant in that agglutination did not occur when using non-pertussis serum in 1 to 4 and 1 to 8. This agglutination reaction is, therefore, very strong evidence that Bordet's bacillus is the causative factor of pertussis.

EXPERIMENTAL WORK

The following experiments are of interest in connection with the use of pertussis vaccine. Dr. J. Freeman[3] of London conducted an exceedingly well-controlled series of cases. The controls in this series received injections of sterile salt solution instead of the vaccine, and the results were as follows:

Class.	Vaccine.	Controls.
Much better	31.0	21.55
Better	37.1	34.55
Unchanged	15. +	23.9
Worse	15.2	18.15
Much worse	1.0	1.85

His routine dose was five million; he then dropped to two and one-half million, then rose to twenty million.

3. Freeman, J.: Brit. Med. Jour., 1909, ii, 1064.

Pfaundler and Schlossman, in their work on children's diseases, give the average duration of pertussis in light uncomplicated cases as varying between eight and twelve weeks.

Holt gives the average duration of the disease as eight to nine weeks, while in the more severe cases, especially during the winter months, it may be prolonged to three or four months.

DRUG TREATMENT

Until the time I began the vaccine treatment, my best results had been obtained from the use of antipyrin combined with sodium bromid, given for one week, alternating with quinin bisulphate given for one week at a time, 2 grains of the antipyrin and 5 grains of the sodium bromid being given every four hours to a child of 3 to 6 years of age, while in infants from 6 months one-half grain of antipyrin and 2 grains of sodium bromid, the dose being slightly increased up to the third year. From 8 to 16 grains of quinin bisulphate per day were given alternate weeks, and all patients were told they should constantly wear a tight binder. This treatment is advocated by Kerley. Besides the above-mentioned treatment, malt and cod-liver oil were given during the spring and winter months. Although the cases improved steadily, the paroxysms decreasing in severity and number, the vomiting becoming less, under the use of these therapeutic agents, even the mild cases lasted from seven to twelve weeks and the severe cases longer.

VACCINE TREATMENT

Thirty-three cases of whooping-cough were treated with the pertussis vaccine, and in all the effect of the vaccine was to diminish markedly the number and severity of the paroxysms and the amount of vomiting.

Absolutely no untoward effects from the use of the vaccine were noted. There were no complications in the cases in which the vaccine was used. No abscess formation, or even slight temporary inflammation or swelling at the site of the injection, and no general constitutional symptoms occurred. The longest time any of the children coughed was twelve weeks and four days. The longest time any child coughed after it was put under vaccine treatment was nine weeks and one day, the average length of time being four and one-half weeks. The injections were given every two or three days in most of the severe cases, and in the very severe cases every day for a few days, until the symptoms were relieved; the milder cases did not receive the vaccine so often nor so much at a time.

In giving the vaccine I was guided more by the severity of the disease than by the age of the child. The youngest child treated was 1 month old and the oldest was 6 years. Most of the children were from

6 months to 3 years of age. The dose of the vaccine varied according to the number and severity of the paroxysms, from twenty million bacteria in the mild cases to sixty million in the severe cases.

The cases that were seen early in the attack, before the paroxysms had attained their height, seemed to respond more quickly to treatment and their course was shorter. In all cases, however, after one to three injections, the number and severity of the paroxysms was markedly lessened.

Some children seemed to respond better to treatment than others, and I attribute this to the fact that the dosage was given irrespective of the age; therefore, the younger children got a larger dose proportionately, and as a rule these latter were the ones that responded most quickly to the vaccine and had the shortest attacks after treatment was begun. This fact is important, since (heretofore) these young babies are so apt to have pneumonia complicating or accompanying pertussis, with fatal results.

It was found that the children did better when the vaccine was given in moderately large doses at frequent intervals of one or two days. A good example of this is Case 30, a child 14 months of age, which received 220,000,000 bacteria or about forty million at a dose, about every two days for two weeks. This child had been coughing and vomiting for two weeks and was cured in two weeks, the vomiting having stopped on the ninth day after treatment was begun. Another very severe case was Case 31, a child a year old that had from twenty to twenty-four paroxysms during the day and as many or more at night, with a great deal of vomiting. This child had been coughing for six weeks when it came for treatment. Forty million bacteria were given about every three days, 320,000,000 in all, in four weeks, the time it took to effect a cure. Case 32 is a somewhat similar case, although an older child with paroxysms not so frequent; it got the vaccine every two days for three doses and then for every three days.

Case 20 was put on the vaccine at once and was ill for only two weeks and one day. Only sixty million bacteria were given, in three doses, but the child was only 7 months old.

The pertussis vaccine, at my suggestion, is now being put up in bulbs of fifty million to the c.c., and I believe the results with this more concentrated vaccine and the larger dosage ought to give considerably better results than I obtained, since in a number of my severe cases I found that forty million to sixty million bacteria at each injection were necessary to control the paroxysms and bring relief, and my opinion was confirmed that larger doses should be given and would effect a more rapid cure. The correct dosage for the mild cases is fifty million bacteria given every other day, while in the severe cases this amount should be

SYNOPSIS OF CASES TREATED WITH PERTUSSIS VACCINE

Case No.	Age.	Month of Year Sick.	Duration Before Vaccine.	Paroxysms		Vomiting.		Vaccine.		Dose-Interval,	Vomiting Ceased,	Duration Disease After Vaccination.
				Day.	Night.	Day.	Night.	No.	Dose, Mil.	Days.	Day.	
1	4 wks.	June	1 wk. 5 days	24	23	Yes	Yes	10	20	3	4	4 wks 1 day
2	3 yrs.	June	4 weeks	20	20	Yes	Yes	7	20	4	8	4 wks. 3 days
3	7 mo.	June	5 wks. 3 days	30	30	Yes	Yes	10	20	4	25	5 wks. 1 day
4	8 mo.	June	3 days	10	7	No	No	7	20	3	..	5 weeks
5	5 yrs.	June	.....	20	12	No	No	4	20	4	..	5 wks. 4 days
6	3 yrs.	June	3 weeks	8	4	No	No	5	20	5	..	5 wks. 1 day
7	4 yrs.	Mar., Apr., May	3 wks. 3 days	6	10	No	No	8	20	7	..	9 wks. 1 day
8	4 yrs.	Sept., Oct.	2 wks 3 days	12	12	Yes	Yes	6	40	3	18	4 wks. 1 day
9	1 yr.	Aug., Sept., Oct.	3 weeks	8	5	Yes	Yes	12	20	7	42	7 wks. 3 days
10	3 yrs.	Sept., Oct.	2 weeks	8	16	Yes	Yes	6	40	4	26	3 wks. 3 days
11	2 yrs.	Aug., Sept.	1 week	8	12	No	No	6	20	7	..	5 wks. 4 days
12	14 mo.	Sept., Oct.	.....	12	16	Yes	Yes	7	40	3	20	3 wks. 2 days
13	30 mo.	Sept., Oct.	2 weeks	9	12	No	No	10	30	3	..	6 wks. 3 days
14	8 mo.	Sept., Oct.	2 weeks	12	9	Yes	Yes	8	40	3	9	4 wks. 1 day
15	6 yrs.	March, April	.....	2	10	Yes	Yes	4	20	7	35	5 wks. 4 days
16	30 mo.	February	7 weeks	6	4	Yes	Yes	5	40	1	5	7 days
17	20 mo.	March	.....	12	6	Yes	Yes	3	20	3	2	8 days
18	9 mo.	April, May	.....	20	12	Yes	Yes	4	20	4	17	5 wks. 3 days
19	24 mo.	April, May	.....	6	6	No	No	4	20	6	..	3 wks. 4 days
20	7 mo.	May, June	.....	12	3	Yes	Yes	3	20	3	4	2 wks. 1 day
21	2 mo.	March	5 weeks	3	2	Yes	Yes	9	20	3	..	3 wks. 3 days
22	30 mo.	March	5 weeks	4	3	Yes	Yes	6	40	3	7	3 wks. 1 day
23	4 yrs.	March	4 weeks	24	24	Yes	Yes	8	40	3	15	3 wks. 1 day
24	3 yrs.	Jan., Feb.	5 weeks	12	24	Yes	Yes	10	20	3	12	4 wks. 4 days
25	2 yrs.	Jan., Feb.	4 weeks	24	4	Yes	Yes	7	40	3	14	2 wks. 3 days
26	4 yrs.	April, May	4 weeks	12	4	Yes	Yes	6	40	3	18	3 weeks
27	6 yrs.	January	2 weeks	6	2	Yes	Yes	4	40	2	7	1 wk. 3 days
28	3 yrs.	Jan., Feb.	5 weeks	8	5	Yes	Yes	11	40	2	16	3 wks. 6 days
29	2 yrs.	May, June, July	2 weeks	8	6	Yes	Yes	6	20	6	28	6 wks. 5 days
30	1 yr.	May, June	2 weeks	6	4	Yes	Yes	6	40	2	9	2 weeks
31	1 yr.	July	6 weeks	20	24	Yes	Yes	6	40	3	10	4 weeks
32	3 yrs.	May, June	5 weeks	6	12	Yes	Yes	9	40	2	2	4 weeks
33	3 yrs.	Jan., Feb.	5 weeks	12	24	Yes	Yes	7	40	3	14	4 wks. 4 days

given every day, or one hundred million every other day. The vaccine is given under antiseptic precautions, subcutaneously, with the ordinary glass syringe, the injection being given in the abdomen or buttocks.

PROPHYLAXIS

A very interesting fact is that prophylactic treatment was instituted by giving immunizing doses of pertussis vaccine to children in a family in which one of the children was under treatment for whooping-cough. These children were watched over a period of two months, and although they had never had whooping-cough and were constantly exposed to the disease, did not contract it. It would seem, then, that the vaccine confers immunity to the child injected with small doses. One child of 5 years was given four injections of twenty million bacteria each, over a period of one month; another in the same family, 3 years of age, got nine injections of twenty million each, over a period of one month; neither child developed pertussis.

Ladd[4] reports nine cases of pertussis which he treated with vaccine, beginning with rather small doses and running up to twenty million, and in four cases to forty million bacteria at a dose, to babies 9 months of age. A minimum interval of five days was allowed between the injections, but in some cases the interval was lengthened to ten days or two weeks or longer. As a result of his investigation he concludes that in another series of cases he would give larger doses at shorter intervals.

When we consider how many of these cases of whooping-cough drag on for weeks or months and how many cases in infants terminate fatally from complications—since in the year 1908 in the registration area of the United States there were 4,969 deaths from whooping-cough, or eleven out of every 100,000 of population, practically the same number as died from measles and nearly as many as die from scarlet fever—it is not too much to say that the vaccine treatment of this disease should ever be in our minds, and should be given a fair and thorough trial and should also be given as a prophylactic measure to immunize children exposed.

Since writing this paper an article[5] has come to my notice. Three patients of the Boston City Hospital died of uncomplicated whooping-cough. An examination of their tracheas and lungs was made by Mallory and Horner, and it was found that these cases presented lesions which involved the ciliated epithelium lining the trachea and bronchi and which appear to be peculiar to this disease.

These observers found large numbers of minute bacteria between the cilia of many of the cells lining the trachea. This microorganism in

4. Ladd: Arch. Pediat., August, 1912.
5. Mallory and Horner: Jour. Med. Research, 1912, xxvii, No. 2, p. 115.

most instances extended to the base of the cilia, the long axis extending in the direction of that of the cilia.

Masses of bacteria similar to those between the cilia were found in the secretions of the trachea and bronchi.

The organism found was a Gram-negative, minute, ovoid bacillus, which suggests strongly the bacillus discovered by Bordet and Gengou in 1900 and afterwards in 1906 obtained in pure culture. They are probably an identical organism. The above-named observers believe this organism to be the cause of whooping cough.

From these studies of Mallory and Horner it would seem that the action of the bacilli in the respiratory tract is apparently almost purely mechanical, because the presence of large numbers of these micro-organisms between the cilia interferes with their action and checks the normal expulsion of secretion. These bacteria also cause irritation, and this in turn brings about coughing and the characteristic whoop or spasm.

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METABOLISM OF A CHILD WITH COMPLETE ABSENCE OF THE BILE FROM THE INTESTINES *

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CASE HISTORY

George M., aged 4 years, entered the Children's Ward of the Massachusetts General Hospital, Sept. 28, 1912.

Family History.—The child had been exposed to a tuberculous grandfather and to a tuberculous friend of the family, who cared for and slept with him at times.

Previous History.—The child was born at term by a normal delivery and weighed 6½ pounds. He was breast-fed for seventeen months, was then given infant diet and did well. In the past year he had four digestive upsets accompanied by light colored stools, but not by jaundice. His appetite has always been irregular, at times ravenous. He had a fondness for sugar and candy, which was freely indulged.

Present Illness.—His mother noticed a tumor in right upper abdomen two months ago, since when it has increased somewhat in size. The child has grown thin, has lost his appetite, has night sweats and fever, but has had no pain; micturition has been normal, and his bowels have moved daily. The stools have recently been light colored but there has been no jaundice.

Physical Examination.—Temperature 99 F.; Pulse 100; respiration 25. He was fairly developed and weighed 13 kilos, which is 3 kilos below the average at 4 years; otherwise was normal except for the abdomen which was protuberant and 52 cm. in circumference at the umbilicus. The hepatic dulness began at the upper border of fifth rib and extended 0.5 cm. below the costal border in the nipple line where the edge was distinctly felt. This edge could be followed to the left upper epigastrium. The spleen was palpable 0.5 cm. below the costal border in the midaxillary line. The left kidney was not felt. In the right abdomen was visible a tumor which extended from just below the costal margin to just above the iliac crest; it was dull on percussion, firm, and gave a definite resistance on deep palpation. The tumor fairly filled the right flank but there was no marked fulness or resistance in the right costovertebral angle. The tumor could not be made out to move with respiration; there was no pulsation and no tenderness. No other masses and no fluid were made out.

The blood was normal except for a slight secondary anemia.

The Von Pirquet test was negative.

The urine was normal in color, clear, acid, specific gravity 1,022, no albumin, no sugar, the sediment was normal.

The stool was brown, soft and formed. On microscopic examination no excess of fat, starch or meat was found. No ova or parasites were seen.

The roentgen ray examination of the abdomen showed a large diffuse shadow in the right upper part which suggested a tumor.

The patient was transferred to the genito-urinary service with a diagnosis of embryonic tumor of the right kidney.

Operation.—Exploratory operation by Dr. Hugh Cabot disclosed a cyst the size and shape of a large grape fruit, adherent to the liver above, to the colon on the inner side, and to deep structures posteriorly. Superiorly a prolonga-

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tion of the cyst extended behind the liver. The gall-bladder was normal, the right kidney was normal. As it was impossible completely to remove the cyst, it was evacuated of one pint of greenish viscid bile, a considerable portion of the cyst wall removed, the cut edges sutured to the peritoneum and abdominal wall, wick inserted and wound closed.

PATHOLOGICAL REPORT

The pathological report was as follows: Fluid from cyst shows no growth on culture. The specimen consists of the walls of a cyst showing reddish brown patches of small size scattered over one surface. Microscopic examination shows a fibrous tissue structure containing blood-vessels and having on one surface small areas of high columnar epithelium. Between the areas of epithelium are areas of granulation tissue. The histologic examination suggests a gall-bladder with chronic inflammation.

After operation the wound drained bile profusely, the stools became and remained bulky, clay colored, almost white, and had a metallic luster, an acid odor and acid reaction, and on all but a few occasions were free from bile. Microscopic examination of the stools showed a great excess of fats, no starch and no meat fibers. The child lost weight for a month and then on reduction of the fat in his diet steadily gained. He was at no time jaundiced and the urine never showed bile.

METABOLISM PERIOD

A three-day period for the study of fat and nitrogen metabolism was begun November 2. In the method used, that of McCrudden,[1] all the food is weighed, and fractional parts of all portions are mixed together for analysis. This admits giving a well-balanced diet composed of foods a child should properly take and avoids the discomfort and uneven results of special metabolism diets. This child was given cereals, bread, potato, fat-free milk, eggs, custard, chicken and small amounts of butter. He was sufficiently well trained to dispense with the metabolism bed.

The excreta were collected, urine and stool separately, the feces weighed and put on the water-bath for evaporation. Nitrogen estimations on the food and stools were made by the Kjeldahl method; nitrogen of the urine was estimated by the Folin-Farmer method; total fat analysis of the food and stool, with estimation of the fatty acids, by the Folin-Wentworth method.

In the following tables are given the results of the analysis:

TABLE 1.—ANALYSIS OF FOOD INTAKE FOR THREE-DAY PERIOD

	Gm.
Total food dried	944.
Fat—per cent.	12.
Fat—total amount	112.
Fat—daily average	37.30
Nitrogen, per cent.	3.17
Nitrogen total	29.90
Protein total	189.50*

* The total protein was estimated by multiplying the amount of nitrogen by the factor 6.34.

1. McCrudden: Jour. Med. Research, 1903, iv, 135.

TABLE 2.—Analysis of Stool Excretion

	Gm.
Total dried stool	87.
Nitrogen—	
Total	2.17
Daily average	0.72
Fat (per cent. of dried stool)—	Per cent.
Total fat	58.
Fatty acids (64 per cent. total fat split)	37.
Neutral fat	21.
	Gm.
Fat—total amount	50.5
Daily average	16.8

TABLE 3.—Urinary Excretion

Amount, c.c.	Nitrogen, gm.
Total amount 2050	19.63
Daily average 683	6.54

TABLE 4.—Absorption and Retention

	Nitrogen, Gm.		Fat, Gm.	
Intake	29.90		112.0	
Output—				
Urine	19.63		.....	
Stool	2.17		50.5	
Absorption from intestine.	27.73	(92%)	61.5	(55%)
Retention (per cent. of intake)	8.10	(27%)		
Loss from intestine 45 per cent.				

The weight of the child increased 150 gm. during the metabolism period.

TABLE 5.—Comparison of Caloric and Proteid Intake to the Average Requirement for the Age and Weight[2]

	Total	Per Kilo.
Average daily caloric intake	1540 cal.	118 cal.
Average daily caloric need	975 cal.	75 cal.
Average daily proteid intake	63 gm.	4.8 gm.
Average daily proteid need	49 gm.	3.6 gm.

It will thus be seen, by comparison[3] with the figures of Czerny and Keller,[4] that the nitrogen absorption (92 per cent.) and its retention in the body (27 per cent.) were not at all disturbed. (Czerny and Keller, 83-95 per cent.)

There was, however, a marked disturbance in the absorption of fat from the intestine. As against the normal absorption of 88 to 96 per cent. as found by Rubner and Heubner,[5] Freund[6] and L. F. Meyer,[7] there is in this case absorption of only 55 per cent.

2. Camerer (through Morse): Internat. Clinics, 1905, ii, Fifteenth Series.

3. There are, so far as I have found, no data on the nitrogen and fat metabolism in children of this age. The normal figures here given are for younger infants.

4. Czerny and Keller, and Von Noorden: Metabolism and Practical Medicine, iii, 853.

5. Rubner and Heubner: Ztschr. f. Biol., 1897, No. 38, p. 315.

6. Freund: Biochem Ztschr., 1909, No. 16.

7. Meyer, L. F.: Biochem. Ztschr., 1908, No. 12, p. 422.

Bile was not found present in the stools during the experiment, nor for several days before and after the period. The mercuric chlorid test was used.

The test for urobilinogen in the urine was constantly negative. According to the theory advanced by Muller, urobilinogen is formed only from bile pigments subjected to bacterial action in the intestine. This has been proved, according to Chase,[8] by experimental work on dogs having the common bile duct ligated. In these dogs urobilinogen disappeared on the fourth day after ligation of the common duct. In this patient, therefore, the absence of the bile from the intestine is further confirmed by the negative Ehrlich reaction for urobilinogen.

That the pancreatic function was normal is shown by the following:

1. Sugar was at no time present in the urine.

2. Neither meat fibers nor starch appeared in the stools.

3. Protein metabolism was normal.

4. On giving a Sahli glutoid capsule a positive test for salicyluric acid was obtained in the urine in six hours.

5. The nuclei of pieces of thymus gland fed to the patient were completely digested.

The child was last seen Feb. 13, 1913. He weighed 15 kilos, looked well and had a hemoglobin of 85 per cent. He had been on a diet containing very little fat. The wound was draining bile at about the same rate as when in the hospital; the abdominal examination disclosed nothing new.

The stool was bulky, whitish, shiny and acid. It showed, under the microscope, a great excess of fat, chiefly as soaps. The test for bile by mercuric chlorid was negative.

The urine was normal. The test for urobilinogen was negative.

CONCLUSIONS

From the study of this case of absence of bile from the intestinal tract the conclusions are:

1. Nitrogen metabolism is normal.

2. Fat metabolism is greatly reduced; the presence of bile is necessary to normal fat metabolism.

3. A child, not otherwise ill, but unable to digest fat on account of absence of bile from the intestine, can, if stomach and pancreatic functions are normal, digest sufficient protein and carbohydrate to maintain nitrogen equilibrium and to gain weight.

4. The negative urobilinogen test is evidence of complete absence of bile from the intestine.

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8. Chase: Jour. Am. Med. Assn., 1912, lix, 329.

THE SCIENTIFIC BASIS FOR THE ARTIFICIAL FEEDING OF INFANTS*

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The inability of many women to nurse their infants is usually regarded as an evil of modern growth and development. This is probably not the case, if one may judge from occasional references to the subject in the Bible, in the writings of Tacitus and elsewhere. But any particular mention in old literature of children is almost lacking, and they were not apparently matters of much concern to people in general until the few last centuries. The references to children before that time are almost entirely of a sentimental nature or by some moralist urging reform and regeneration, and inveighing against the wickedness of modern days. While we are informed that many mothers did not nurse their children, we cannot learn from the general diatribes whether it was because they could not or would not do so.

But whatever the reason why a woman did not nurse her infant, two methods have always been possible by which to supply him sustenance — the employment of a wet-nurse or some form of artificial food, in almost all instances the milk of a domesticated animal. Until the nineteenth century, the former of these was the only method of general application. For, if the prevalent superstitions, that a child might acquire from animal's milk some of the physical characteristics of that animal in the shape of a stray beard or horns, were disregarded, any slight experience with artificial feeding showed the direful consequences to the infant. It was a misnomer to call it "bringing up by hand" because in this way children were not brought up. Apart from lack of information as to the quantity and quality of food, there was a total ignorance in regard to cleanliness. It seems strange, but not unlikely, that any form of artificial feeding would have failed in those days on account of the lack of proper utensils. Horns for bottles with sponges and pieces of perforated leather for nipples, hardly meet what we look on now as necessary requirements.

Artificial feeding was then, as now, chiefly necessary in cities, and the milk-supply of cities was absolutely bad. The unfortunate and diseased animals that furnished the milk were kept in the filthiest of buildings, often with no light or ventilation, were covered with sores

*A lecture delivered before the Harvey Society of New York, March 29, 1913.

and had usually for their only food the fluid refuse from breweries. But the evils of wet-nursing were so appreciable that a substitute for it was constantly sought and attempts were made with artificial mixtures of various kinds. Gradually, in a purely empirical way, the most unsuccessful of these were eliminated. But it was not until after the middle of the last century that artificial feeding was largely used. But anything more than empiricism has been of very recent date, and it is really only in the last twenty years that much that can be dignified by the word scientific, has been learned about the nutrition of infants.

It would not be too much to say that the majority of artificial feeding has been done and still is done empirically by rule of thumb, and with excellent results. Empiricism here has frequently shown the way before there has been satisfactory explanation of the *modus operandi* of some procedure, while, oftentimes, the explanation generally accepted, has required revision though the fact established by observation has remained. Nevertheless, empiricism has also been responsible for the prevalence of many false ideas that have been rooted out only with great difficulty. Probably the reason for this is that the healthy infant has a great margin of safety. The flame of life, though small, burns fiercely within him. He will thrive at times under the most adverse circumstances and will withstand a great amount of well-meant but misdirected attention. The distinction is not sharp between what may allow of satisfactory development and what produces it.

There is only one safe criterion of the proper food for an infant. It must so further his nutrition that he will leave the period of infancy and enter into that of childhood with an entirely normal mental and bodily development. If a decision as to the value of a diet were reached in this way, after long observation and with sharp criticism as to any deviation from the normal, there would not be so much difference of opinion as to proper methods. By clinical observation and not by physiological or chemical determinations must the superiority or inferiority of a diet or of a method of feeding eventually be established, and the acuteness of observers varies and their conclusions may be widely divergent.

When artificial feeding is begun, one of the first problems that presents itself, is the total quantity of food that should be given to a normal infant, sufficient to supply his maintenance requirements and his requirements for growth. With the majority of breast-fed infants this does not have to be considered. The infant nurses until his appetite is satisfied, and the appetite and the quantity of milk are in most cases so nicely regulated that the demands of one are supplied by the other. But with the bottle-fed infant, the danger of overfeeding or underfeeding is real. The child's appetite, though still a guide, is not so much to

be relied on, and what might be regarded as hunger is often discomfort from too much food.

How then are we to judge of his requirements?

The answer to this question has been sought in three ways: by metabolism experiments, by the determination of the energy exchange and by the so-called "statistical method," or the balancing of the intake over long periods of time with the calculated output obtained by the occasional estimation of the excreta.

Metabolism experiments do not offer a satisfactory solution of the question for the chief reason that they can be of only short duration compared with the whole period of infancy. This would mean the application of the conclusions of a few days to a period many times that length, the continuance of what might temporarily be borne to a point of intolerance and the multiplication of any false conclusion or trifling error to a substantial amount.

Metabolism experiments show excellently whether a food is distinctly deficient; they are not designed to show that an excess is given unless this excess is very great, and they are not at all well adapted to determine the food requirements.

Partly with the idea of determining food requirements, Rubner and Heubner first studied the energy exchange of infants with a Petenkofer-Voit apparatus. In order to judge whether their results are to be taken as universally applicable, it is necessary to remember that the observations cannot be continuous. They must be interrupted every four hours in order that the infant may be fed, and once a day for a longer period. It is, therefore, impossible to make the determinations during more than twenty hours out of the twenty-four, and these four lost hours differ very greatly from the others in the activities that go on in them. The infant is much more active outside of his restraining frame than when in it. With the Petenkofer-Voit apparatus the metabolism of quiet and active periods could not be separately measured, consequently it was assumed that there was not much difference between them and that the muscular activity of an infant had a negligible influence on the total metabolism.

Working with Dr. Lusk's calorimeter of the Atwater-Rosa-Benedict type, which was especially built for use with infants, I have shown that activity has an unexpectedly great influence; that crying increased the heat elimination of one infant 18 per cent., and that of another 39 per cent. It is very apparent, therefore, that if the determination of active periods is lost, the error may be a large one and it is also apparent that the metabolism may vary greatly from day to day, according to whether the infant is especially quiet or especially active. It is quite obvious that experiments necessarily conducted in this manner, cannot furnish the

information that is required as to the heat elimination of infants under normal conditions, and so the amount of potential energy that they require.

Determinations of the energy exchange may be made during sleep with a high degree of accuracy, using the modified Atwater calorimeter. I have made many such determinations and have obtained concordant results, provided the conditions were the same as to diet and that the infants were asleep. Any deviation from these conditions allows of no comparison between different infants or between different periods with the same one. With this method then, we may obtain valuable information as to the effect of different kinds of food, of different environment and perhaps of different pathological conditions, but we cannot learn the total amount of energy that should be furnished the normal growing child.

The statistical methods consist in determining by actual weighing the daily intake of infants over long periods of time. A small number of observations have been made in this way by physicians, chiefly on their own children. Occasionally, the urine and feces have also been examined. But while the weighing is accurate, the variations in the composition of breast milk make it practically impossible to draw conclusions as to the total food value of the amount ingested, even if frequent samples are taken for analysis. The composition of breast milk is different to a marked degree at the beginning and end of each nursing period, and may be different at each period. If we rely on this method for information as to the total energy that should be furnished to an infant in his food, it makes a great deal of difference whether we consider, as Heubner did, that the caloric value of a liter of breast milk is 650 calories, or with Schlossman, that it is 782 calories.

The statistical observations have been almost without exception on breast-fed infants. It seems to me that there is a distinct opportunity offered to make the same observations much more easily and accurately on the bottle-fed, especially if the feedings are made up in a milk laboratory and the various ingredients carefully measured. It would then only require that the children should gain sufficiently and regularly. They will not do it for a prolonged period of time in hospitals, and such observations are impossible there. Here is the chance for the practicing physician to furnish information that may be of great practical use.

With all its sources of error this statistical method, which is really a refined empiricism, offers a better means of determining the average requirements of infants than do the others, and it is only the average that can be determined. No two infants even of the same size and weight have the same requirements. I have found that a healthy infant when asleep has a heat production of 1,094 calories a day, calculated in

terms of square meter of body surface. But when infants are awake, a variable factor is introduced; for their activities are never the same, and these cannot be controlled and cannot be measured. For this reason it is never possible to say with certainty how much food any one particular infant will require. The problem of determining accurately the requirements of infants has not remained unsolved for lack of trying. The trouble lies in the inherent difficulty of the problem itself.

Before discussing the influence of various foods on digestion and metabolism, I should like to say that it is obviously impossible to give even a sketch of the whole field. I shall, therefore, confine myself to a consideration of those aspects that chiefly have claimed and do claim at present the attention of pediatrists. And I shall not attempt systematically to outline the uses of the food-stuffs or the transformations that they undergo, but rather to point out in what way it is believed they may be harmful and the proof that is brought that they are.

In the study of infant feeding it is to the several components of the milk that attention has especially been directed. The endeavor has been from the beginning to find out why it is that children fed on human milk thrive almost without exception in a satisfactory manner, while those that receive cow's milk may, oftentimes, do so badly that either extensive modification is necessary or a change to some other form of food. Ten years ago the answer to this seemed perfectly plain. Chemical analysis showed as the most striking difference in the composition of the two milks that the protein of cow's milk was present in three times greater quantity than in human milk and that the proportion of casein to lactalbumin, was much greater in the former. It appeared logical to suspect the casein as the substance most difficult of digestion and when Biedert, by means of reactions which cannot now be looked on as conclusive, determined what he considered to be undigested casein in the stools, it was generally assumed that the excess of protein in cow's milk was the explanation of the failure of cow's milk as a food for infants. In spite of the objections that were raised to this opinion, it was the prevalent one for many years, and has been given up reluctantly. For to a certain extent the belief seemed supported by the theory of Hamburger that *"Artfremdes Eiweiss"* is an irritant to the especially sensitive cells of the infant's alimentary tract and that the necessity of breaking down the protein molecule to such simple substances that they could not be injurious after absorption, threw an added burden on the digestion, and one which was unnecessary with milk of the same species.

Support was also offered by some of the experiments of von Behring on the permeability of the gastro-intestinal tract of the young for bacteria and his insistence that finely divided casein could pass through the coarse filter of the intestinal wall. But the experiments of Bahrdt and

Langstein on newly-born children have proven Hamburger at fault, for they have shown that the gastro-intestinal tract of the young does not treat in a different way *"artfremdes"* and *"arteigenes Eiweiss"*; it breaks both down to albumose in the stomach and to amino acids in the small intestine. Von Behring's views are also not possible of acceptance. If unaltered cow's casein were regularly absorbed, it would cause the production of an antiserum to cow's casein with the regularity that the parenteral injection of this substance does in experimental animals. Only in a few instances have precipitins for cow's milk been found in the blood of marantic children, by Moro and Brauer; but it is a very unusual finding compared with what one would expect if the absorption of the unchanged casein were of frequent occurrence. And a certain degree of increased permeability in the very ill or moribund is not to be wondered at. Uffenheimer has emphasized the very perfect provision of the body against such an occurrence as the absorption of foreign protein by the prompt and complete precipitation of the casein by rennet in the stomach and of the protein substances out of the gastric contents, when they reach the intestine, by the cholates of the bile.

But it has been shown also that the observations of Biedert were false. The small white or yellowish masses which he considered to be undigested casein have been determined to be the insoluble soaps of the fatty acids, and indeed are much more frequently found with breast than with artificial feeding. Adler has shown that the precipitate, the result of the addition of acetic acid in the cold, was not composed of casein, as Biedert and Albu and Calvo had insisted. The nucleoprotein of the intestinal secretion and the nucleoalbumin of the bile react in a like manner. He also showed that fasting stools contained a similar substance and that the minute quantities of albumin, albumoses and amino acids that were present were common to the stools of breast-fed and artificially-fed children alike. Numberless metabolism experiments have demonstrated in addition, that the nitrogen of cow's milk is absorbed and retained, within the limits of experimental error, as satisfactorily as that of breast milk. The assumption, therefore, that cow's casein is difficult of digestion, appears in the stools as such and composes a *"Schädlicher Nahrungsrest"* is unsupported.

It should be mentioned, however, that casein does at times appear in the stools. The pretty experiments of Talbot have determined this. Occasionally when children are fed on raw milk, large bean-shaped, firm masses are found in the stools. These are largely composed of protein containing in its meshes neutral fat. The proportion of protein in these curds is so large as to make it impossible that it could come from the intestinal secretions, and Talbot was able to demonstrate that the protein was casein by precipitin tests in which the dissolved protein was pre-

cipitated by anticow-casein serum, in the same way that pure cow's casein was precipitated, while no precipitate was obtained with other stools. Uffenheimer, later, also showed their biological character by anaphylactic tests, so that it may now be regarded as certain that cow's casein may appear practically unchanged in the stools. But that it has a limited if any pathological importance, but rather depends on physical conditions in the gastro-intestinal tract, may be assumed from the fact that these curds can be caused to disappear by boiling the milk, as a consequence of which the precipitation of casein by the rennet occurs in much finer flakes, and that infants passing even a large number of such curds present usually no evidences of discomfort or other derangements of digestion.

From numerous metabolism experiments it appears undoubted that, with this exception, the nitrogenous constituents of the food even when that food is cow's milk are completely absorbed and that the nitrogen of the feces comes almost entirely from the intestinal secretions, and from bacteria. The nitrogen in 100 grams of the dried feces of the breast-fed infant is practically as great as that in the feces of the artificially-fed, when allowance is made for the slight differences that occur from time to time with any feeding and with any child. Indeed, when equal amounts of protein are given, the amount of nitrogen may be greater with the breast-fed child, as a result of the excess of fat in breast milk, which causes an increase in the intestinal secretions.

From an examination of the stools, therefore, we obtain no clear indication that the protein of cow's milk is more poorly digested or absorbed than is that of breast milk.

But the chief interest attaches to the retention of the nitrogen. One of the most striking facts in this connection is the extraordinary eagerness with which all infants retain nitrogen. Growth is as normal and necessary a process for them as is the maintenance of equilibrium for an adult. The child's attempts to grow cease only with life itself. For this reason, he retains nitrogen and the other substances necessary to form his protein material, if it is any way possible, and continues to do it under the most discouraging circumstances. Even when receiving a food the caloric content of which is insufficient for his requirements, he retains nitrogen and a not inconsiderable quantity of this, and burns his stored-up glycogen and fat to compensate for the lack of energy supplied in his food. Instead of utilizing all the food ingested to furnish energy as would the adult, he continues to use some nitrogen for growth and sacrifices other tissues of his body for this purpose. In other words he grows at the expense of his general nutrition.

This statement has been repeatedly proved by metabolism experiments, but clinically the fact is also appreciable, for children, not gain-

ing or even losing weight, may continue to grow, at a diminished rate to be sure, but nevertheless, to an extent that can be measured.

The protein food that is taken serves three purposes: first, it replaces that which has been used in the performance of the ordinary functions of the body and lost as desquamated cells, and as secretions; second, a small part is burned to furnish energy, and third, a distinct amount is retained for growth, often 50 per cent., and even more.

It has been impossible up to the present time to contrive any experiments that will determine the amount used in the wear and tear of the body and that part destroyed for the production of energy. It is clear, however, that if the diet contains other ingredients in proper quantity and quality the amount of protein destroyed for these purposes is not large. The total amount of protein which is requisite, requisite and no more, is similarly undetermined. There is very reason to believe that the amount furnished to a healthy nursing infant represents at least a sufficient quantity and cannot be much in excess. As I have said before, it seems assured that cow's protein is not only digested as easily as human, but that the nitrogen of it is retained as readily, and it, therefore, appears not unlikely that other things being equal, less nitrogen might be required with cow's milk for the reason that nearly all of the nitrogen of cow's milk is available for use, while only about 80 per cent. of the nitrogen of human milk is available. The other 20 per cent. is in the form of urea and extractives that can only be at once excreted in the infant's urine. I said other things being equal, for it is not beyond the bounds of possibility that it is advantageous to furnish an artificially fed infant some energy in the form of protein which may be at once used for the production of heat when the gastro-intestinal tract is especially liable to injury from the amount of fat and sugar necessary to produce the heat, with no help from the protein. Except for such a purpose, the protein requisite is strikingly small, and if we may accept the evidence furnished by breast milk, the protein does not require to be greatly increased after the first few months of life until toward the end of the first year. The chief demands for protein are to compensate for wear and tear, and to provide for growth and as the one of these increases the other diminishes. Growth which is most rapid in the early months becomes less and less so, while as the body assumes a larger size, the wear and tear is greater. Thus it comes about that these two demands nearly balance one another throughout a large part of the first year.

The nitrogen retention of the normal infant is dependent to a great degree on the amount of protein food. After partial or complete deprivation of this, he retains a large amount for some time, when it is again offered, as if to make up for that which he had lost. If the protein continues to be given in excess, however, after a few days of very great

retention, the retained nitrogen gradually diminishes day by day to an amount equal to that which would have been held, provided the infant had received the optimum quantity and no more.

But all of the other food-stuffs have an important influence on the retention of nitrogen. With a normal infant receiving enough food to meet his requirements the addition of fat to the diet in any form has no great influence. The addition of sugar or carbohydrates causes a much greater retention. The effect of a disturbance of digestion caused by either fats or carbohydrates is striking, especially when fat is the offending element. A negative nitrogen balance is the result. The loss of nitrogen occurs not only in the feces due to the greater amount of intestinal secretion, but in the urine as well, and to a larger extent. This loss of nitrogen is the result of changes in salt metabolism, for on the unfavorable influence of this the elimination of nitrogen chiefly depends.

But the retention of nitrogen is also largely dependent on mineral metabolism. The retained nitrogen cannot circulate in the blood nor be loosely held by the tissues for any considerable length of time. It must be built up into living protein material and to do this salts must be available. Unless they are available the nitrogen is excreted again. Thus there must be a certain parallelism between the amount of nitrogen and the amount of total ash retained, and this has been found to be so. For every gram of nitrogen about 1.7 grams of ash are retained, not always at exactly the same time, but if the experiments are of long enough duration, these figures hold nearly true. A close parallelism between the retention of nitrogen and that of the individual bases cannot at present be shown, probably chiefly on account of the technical difficulties of the experiments, but also on account of the formation at different times of nitrogenous compounds now richer in one element and now in another.

I have already stated that it is the general belief that the protein of cow's milk is as readily utilized as is that of human milk. Is there then any possibility that it is injurious to the infant in the quantity in which it is given, usually two, three or four times as much as the breast-fed infant receives of human casein? Does this put an excessive strain on the organs transforming the products into eliminable form and those excreting these products? The only answer to this can be that no such injurious effect has ever been noticed.

There is a possibility, however, that a great excess of protein may, under certain circumstances, be harmful. Two calorimetric experiments that I have made indicate this. The heat production of one infant was raised 10 per cent. by an increase of protein in his food and that of another 26 per cent. Moreover, it could be calculated in the case of the second child that all of the extra heat and carbon dioxid could not come

from the protein alone, but that this protein, or more probably its decomposition products, acted as a stimulus to the metabolism of all the foodstuffs. This extra heat produced must be eliminated. Under ordinary circumstances, this is undoubtedly accomplished without difficulty. But if to excessive atmospheric temperature and humidity, factors preventing the elimination of heat, there is added the incurred burden of disposing of an excessive and unnecessary amount of heat, the possibility of nutritional disturbance may be increased.

Two other possibilities have been mentioned as factors causing failure in artificial feeding, one the formation of toxic decomposition products of protein and the other anaphylactic phenomena. The great size of the protein molecule allows of the formation of an enormous number of products, many of which are undoubtedly poisonous, provided the natural defenses of the body are inadequate. But nature has guarded against injury by them in a most thorough manner and though the possibility remains, proof that injury is caused is lacking. Moreover, Ernst Magnus has shown that, after all kinds of feeding, the intestinal contents obtained from an intestinal fistula may be toxic, except on a diet of milk, and then the toxicity is absent.

That anaphylactic phenomena are at all common with cow's milk feeding is much to be doubted. But that they occur as rarities seems likely. The only infant of which I have personal knowledge presenting such symptoms had regularly, severe vomiting after the ingestion of less than one ounce of cow's milk, with an intense urticarial eruption and collapse, and this was repeated as often as the cow's milk was given. No tests were used with this child, nor so far as I am aware have they ever been used to show a hypersusceptibility to casein in the same way that they were by Schloss to show a hypersusceptibility to white of egg. Hypersusceptibility in the biological sense cannot be used to explain the ordinary failures with artificial feeding.

Recently a series of interesting observations has been made by Drs. Holt and Levene and their coworkers on infants that had received a "synthetic" food very rich in casein. After a period of from four to six days on this diet, fever resulted and this continued until the food was stopped, when it immediately subsided. Interesting speculations are at once raised by these results, but they have little bearing on the question of artificial feeding, first on account of the artificial character of the food with its high sodium hydroxid content, and second, on account of the great quantity of casein given, greater by far than could be taken even in undiluted milk.

There is one other possibility that I should like to consider, and that is, that a large amount of protein may play a not inconsiderable part in the production of the symptoms of what Czerny has called *"Milchnähr-*

schaden," and which will be later discussed. It seems not improbable that some of the benefit to be derived from a change to a carbohydrate rich diet in this condition may be due no less to the limitation of protein, and thus of the putrefaction, than it is to the diminution of fats; at least some experiments that I have been conducting point that way. But when all is said, actual and possible, against the protein and especially the casein of cow's milk, it must be granted that it has so far lived down its evil reputation that it is generally regarded as a factor of but little if any importance in the general production of disorders of nutrition.

The differences of opinion that have been entertained in regard to the fat of the food, have been all as to the dangers of it and the disturbances that it might cause. There is unanimity in the belief that fat is beneficial for infants, and that those who, because of nutritional disturbances, cannot take a reasonable amount of it do not thrive so satisfactorily as do those who can. The very large proportion of fat in human milk indicates the amount of energy that advantageously may be provided by fat for the healthy infant. But the difficulty comes in furnishing this to the artificially-fed child without danger. It is necessary to emphasize "without danger" for the reason that the tolerance of infants for cow's milk fat varies to an astounding degree. One will take even more than is found in human milk without a symptom and over a long period of time. This tolerance belongs especially to the older infant though the very young may also exhibit it. Thus R. A. Cooke and I, in the course of some experiments, gave a boy of 10 months 76 grams of fat a day for several weeks. He had no evidence of disturbance, his nitrogen partition was normal, with no increase of ammonia, he gained weight with rapidity and was comfortable.

But another infant, especially a young one, cannot take even a small amount without evidences of its harmful effects. Generally these evidences do not appear at once and perhaps only after a period of apparent benefit. Hence it has come about that there are widely divergent views as to the amount of fat that may be given with safety. To stay within safe limits is eminently the wise thing to do. For an intolerance to fat once established persists longer than an intolerance to any other food ingredient and compels the reduction of the fat to such a low point as to throw the burden of furnishing energy almost completely on the carbohydrates, and carbohydrates in excess are an insecure support for the young infant.

The digestion of fat and the effect of fat on the digestion of infants have been studied with great care by Tobler, Uffenheimer and others. Fats so retard the emptying of the stomach that stagnation may occur, and when the quantity is large, selective retention of the fat takes place. In marked instances of this, at the end of the day, it may be possible to

obtain by the stomach tube almost all of the fat. But given such admirable opportunity for it, vomiting usually takes place. The strong odor of butyric acid suggests that the lower fatty acids are increased. Huldschinsky failed to obtain proof of this in persistently vomiting infants.

Though the presence of a fat-splitting enzyme in the stomach was definitely determined by Sedgwick, it probably plays a very small part, and the splitting of fats is accomplished chiefly in the intestine, and so completely, that under normal circumstances, not more than 1 per cent. of the fat escapes this action. The further fate of the fats is not sufficiently understood. It would be of great assistance to know the form in which they are absorbed. Are they absorbed chiefly as fatty acids or as soaps, and if as the latter, as the soluble soaps of sodium and potassium or the insoluble ones of calcium and magnesium? Are the insoluble soaps the chief and most important means for the absorption of calcium and magnesium, or are they substances incapable of utilization? Are sodium and potassium driven out of combination with the acids, as has been suggested, and replaced by calcium and magnesium in the colon?

Much in regard to the form of fat even in the stools is denied us on account of the difficulty of separately determining neutral fat, fatty acids and soaps. So many methods have been employed each in itself more or less inadequate that a comparison of results obtained by different experimenters is hardly of value. The one good present method, Inaba's modification of the method of Kumagawa and Suto, allows the determination of only total fat. It may be said that approximately 40 per cent. of the stool of the normal infant is fat, and of this, 10 per cent. is neutral fat; about 10 per cent. is soluble soaps and the rest fatty acids and insoluble soaps. The amount and relative proportion of each of these may be greatly influenced by circumstances and the absorption of fat may be similarly influenced. For example, while more than 90 per cent. of the fat is absorbed under normal conditions, less than 50 per cent. may be absorbed with severe diarrhea of gastro-intestinal origin, and the neutral fat instead of being well split and forming only 10 per cent. of the stools may form 40 per cent. or more.

Fat was for a long time disregarded as a cause of harm to the infant. Biedert was one of the first to insist on the part that it might play in the production of diarrhea, but it was Czerny's and Keller's experiments and writings and those of their coworkers that showed unmistakably that fat was a power for harm.

The most discussed and most studied of the conditions ascribed to fat is that called by Czerny, *"Milchnährschaden,"* which he says is synonymous with *"Fettnährschaden."* According to his view, the element responsible for this condition is the fat of the food. Increasing this fat

makes the condition worse, and diminishing it makes it better. Infants with this condition are pale, and while perhaps fat, are pasty. Their appetite is poor, they gain in weight slowly, and finally not at all. The most striking thing, however, is the character of their stools. They are constipated. The stools are large, dry, light colored and foul, the so-called *"Seifenstühle."* The condition is amenable to treatment, and infants with this disorder usually respond rapidly to a diminution in milk and the addition of cereal and sugar especially in the form of one of the malt-soups, a combination of dextrins and maltose.

There are certain definite chemical changes with these *"Seifenstühle."* The nitrogen is somewhat increased, but the general retention of it is in no wise interfered with. The carbohydrates of the feces are very much decreased, or rather, as Usuki has shown, these soap stools only occur when there is less than half of the carbohydrate in the stools that is ordinarily found. The fat is absorbed to a surprisingly good extent. It was held by Freund and others that the absorption was even better than under normal conditions, but the poor methods of analysis allowed this faulty conclusion. We know now that absorption suffers somewhat, but only to a slight extent, so slight, that a lack of sufficient nutritive material cannot account in any way for the clinical picture.

The positive evidence of harm is shown by the study of the mineral metabolism. It is the earthy alkalies that suffer most. Rothberg and Birk first pointed out this fact, the former for calcium and the latter for magnesium, and it has been shown since then, over and over again. Why so much of these earthy bases is excreted is not clear. Bahrdt has calculated that much more calcium is passed in the stools than could be accounted for by the binding power of the fatty acids, but he was not able to determine the form in which this excess of calcium was lost. The fact remains, however, that the calcium and magnesium are not retained. Whether this, the most constant and striking of the findings, is the only explanation of the poor condition of the infant and the failure to gain is not quite clear.

Stolte has pointed out that fat and calcium must be present in the food in considerable concentration in order that soap stools and constipation can result. But putrefaction is also necessary for the production of these stools as opposed to fermentation. Meyer and others have shown that the addition of casein may cause soap stools with evidences of putrefaction. But this excess of putrefaction only takes place when there is an insufficient quantity of carbohydrate in the food. If fermentation is active, putrefaction cannot take place, and without this putrefaction soap stools cannot be formed. Usuki, in studying the partition of fat in the stools, found that when carbohydrate is present in the stool in any quantity, that is, when there is a substance that can ferment, soap stools

are absent. If, however, the carbohydrate is in such quantity or of such quality that it is rapidly absorbed and therefore does not ferment, soap stools may be present.

There are three requisites for the production of these stools; at least a moderate amount of fat, casein and calcium in considerable quantity and the absence of sufficient carbohydrate. This is an excellent example to show how complicated are the conditions in nutritional disturbances and how the food-stuffs interact, and how difficult and indeed unwise it is to consider one alone as the cause of any disturbance. The condition is usually considered a *"Fettnährschaden."* One could with nearly as good reason uphold the proposition that it is an *"Eiweissnährschaden,"* while it is presumably more dependent on insufficient or improper carbohydrate than anything else. For the condition can be cured without reducing the fat and protein if the proper amount of suitable carbohydrates is added.

The diarrhea caused by fat is quite a different condition. It is almost always acute and brings about chemical changes quite distinct from those just described. The endeavor was made by Salge to prove an association between a bacillus, the acidophilus, with this condition, but without sufficient evidence. Raczinski has shown in the breast-fed, and Langstein and Meyer in artificially-fed infants, an excess of lower fatty acids in the diarrheal stools. These, by their irritating effect, undoubtedly play an important part in the production of the diarrhea. For a long time the cause of the high ammonia content of the urine could not be explained. Keller unavailingly sought for abnormal acids in the urine. Eventually, Steinitz demonstrated that there is a great loss of alkali, especially of sodium, by the bowel. The body is thereby so deprived of bases with which to neutralize the acids of intermediary metabolism, that ammonia must be furnished to take their place. The condition is therefore a relative acidosis. Though this increased ammonia was originally supposed to be due to the excess of fat, it is really quite independent of it, and occurs with diarrhea due to any cause. Even with a severe diarrhea the calcium and magnesium may be well absorbed and retained. So with these two disturbances that may be due to fat we have quite different chemical changes. One may run its course with a positive sodium and potassium balance, but with a loss of calcium and magnesium, the other with a positive calcium and magnesium balance, but with a loss of sodium and potassium. From their relative importance in the organism we would expect the condition in which calcium and magnesium loss occurred to be better and more persistently borne, and such is true of the clinical course.

The stormy condition sometimes met with as the result of feeding excessive quantities of fat, with sudden onset, high fever, repeated convulsions, persistent lack of appetite, vomiting and diarrhea has found no adequate explanation. It is for lack of a better name often spoken of as "acute acidosis" without evidence that the accompanying acidosis plays more than a secondary and subordinate rôle. Despite the lack of information in regard to it, the condition is a very serious and oftentimes fatal one.

In controversy, the battle usually rages thickest and hottest around some definite point. So it has always been with the question of artificial feeding and so it is now. Proteins and fats are temporarily disregarded and the carbohydrates and salts are the objects of chief attack. With new knowledge and new hypotheses the assault is made from different quarters. The questions at present at issue are not at all those of ten or even five years ago.

Opportunity is given for a great difference of opinion in regard to the sugars and carbohydrates, because their fate in the organism is so little understood and the various intermediary products of their metabolism from the time of their absorption to their complete disintegration to carbon dioxid and water are quite unknown. It is thus not possible to follow these substances to the same extent that it is the proteins and the salts.

For the same reason opinions reached in regard to the carbohydrates must be largely the result of clinical observations. Now, while it is contended that clinical observations may have the same value as laboratory experiments, it can only be so when they are planned with the same care, conducted with the same adherence to technic and with the same avoidance of interfering, extraneous influences, and finally viewed with the same critical skepticism that the trained laboratory worker would employ. Usually these conditions have not been fulfilled, and for this reason from clinical observations absolutely contrary opinions in regard to almost any aspect of the question are obtained. To cite a few examples: It is claimed that lactose is absorbed from the intestinal tract very slowly and is therefore dangerous on account of the rare opportunity that it gives for fermentation. Again, it is asserted that it is dangerous because it is absorbed so rapidly that lactose does not have an opportunity to break it down, and that, after its absorption as such, it acts as a poisonous and pyrogenic substance. Sainmont believes that he has demonstrated by observations on puppies that lactose is a much safer sugar than saccharose or glucose, while Heim came to a totally different conclusion. And in spite of the proof that could be brought against him, Weigert denies that milk-sugar has a nutritional value and insists that as good results can be obtained with milk and cereal mixtures as with

these plus milk-sugar. If one should rely entirely on published opinions, he would be left in a sad state of perplexity.

I do not wish to review matters concerning which there is complete unanimity of opinion, but I should like to emphasize, as so many others have done, the great dependence of the infant on the carbohydrates. He normally, and for his best advantage, obtains a large proportion of his energy from them. For a time he may disadvantageously exist with a minimum of carbohydrate food, but a lack of it very soon threatens life. So long as the infant with a nutritional disturbance retains a certain tolerance for carbohydrates, recovery may take place; but an entire loss of tolerance takes away the possibility of this. Especially in artificial feeding are the carbohydrates of importance; for the infant cannot take, or it is not wise to give him, the amount of fat that the breast-fed infant receives. The deficiency of energy must therefore be supplied largely by the carbohydrates.

There has been, and still is, much discussion as to the form of sugar which is to be preferred for infants. What one is most satisfactory as regards (1) tolerance, (2) influence on gain in weight, (3) influence on the absorption and retention of other substances, (4) influence as a corrective when nutritional disturbances exist and (5) as regards safety.

The disaccharids are the only sugars ordinarily employed in infant feeding, the monosaccharids and polysaccharids have been used only for experimental purposes and need not concern us here. Of the disaccharids, lactose and saccharose are alone employed. Maltose is barred by its considerable cost. An especial place must be accorded to maltose in combination with other substances in the preparations known as dextrimaltoses, *nährzuchers,* malt-soups and various proprietary foods; but it must be recognized that maltose plays only a partial, perhaps an insubordinate, rôle in them. These mixtures contain a multitude of substances, known and unknown, maltose, salts, nitrogen-containing compounds and a great variety of dextrins and substances closely allied to them. And the beneficial results following their use cannot be ascribed to any one particular substance.

It may be said in general that the limit of tolerance for sugars before mellituria takes place is very high in the normal infant. The sick infant, the feeble and premature and the eczematous may excrete sugar in the urine with a very small intake, but this sugar, so far as has been demonstrated, is almost always lactose or galactose, rarely saccharose and never glucose, unless diabetes is present.

This tolerance is so high — Grosz, Nobécourt, Finizio, Aschenheim and others have shown this — as to put the danger of alimentary mellituria for normal children, with a reasonable intake, out of the necessity for consideration. This is the conclusion that one must reach even

though different concentrations have been used and these have yielded different results. But these experiments give us no indication that either lactose or saccharose is superior. The limit of tolerance is about the same for both. That for maltose is twice as high, probably because maltose can be burned after passing the intestinal wall. Lactose and saccharose cannot be burned by the body cells, except apparently in very small quantity and after repeated injections, as Leopold has demonstrated for lactose. The tolerance for the maltose combinations has not been determined.

Under ordinary circumstances, all sugars act satisfactorily enough so far as gain in weight and a favorable influence on the retention of other substances is concerned. There is no convincing proof clinically or experimentally that one is superior to the other. They apparently furnish utilizable energy in the same proportion and their favorable influence on the retention of nitrogen seems to be the same, though experimental evidence for saccharose is almost lacking. After the first few months additional carbohydrates in other forms have a distinctly beneficial effect. Here the malt preparations may find application; but there is no proof that the normal infant may not thrive entirely satisfactorily without them, with the ordinary cereals.

It is, however, in the correction of nutritional disturbances that a great difference between the sugars is seen. The disturbance described by Czerny and Keller as *"milchnährschaden,"* responds promptly to the malt preparations, especially when combined with cereals in considerable quantity, and this more or less irrespective of whether the amount of milk is reduced or not. To increase the lactose or saccharose unless they have been present in very small amount, is a dangerous method to bring about a similar result, because it may cause an excessive fermentation with severe diarrhea. Maltose alone has no advantage over lactose or saccharose in correcting this disturbance as Usuki and Gerstenberger have demonstrated. It is equally if not more dangerous. It is the malt preparations combined with large amounts of cereals that are the most efficacious. Exactly why, no one knows. Usuki found after their use three or four times as much carbohydrate in the stools as when maltose alone was given, so that it might be said that the substance least utilized gave the best results. He believed that the beneficial effect was due to the slow, continuous and never rapid fermentation. On the other hand, DuBois and Stolte maintain that it is the potassium carbonate contained in the malt-soup that is of value, especially in preventing the excretion of calcium. It will take further experiments especially planned to decide this.

It is not so easy to determine what is the safest sugar. The difference of opinion here is very great. There is a tendency at the present time,

even for many who were formerly warm in its praise, to accuse milk-sugar of being a dangerous substance even for normal infants, and of being the cause of most of the nutritional disturbances to which the infant is heir. The complaint is overdrawn. The satisfactory results with thousands in the past and at present prove this. Those who entertain these extreme views in regard to milk-sugar reach them as the result of hospital experiences in which hardly a normal child is ever seen. They forget the good results with healthy infants. Those who would deny milk-sugar any place in the dietary of infants must take the stand that it is dangerous only on account of its combination with cow's milk. For the milk-sugar of all animals is identical and nutritional disturbances are most promptly and permanently cured by breast milk in which milk-sugar is in greater proportion than is found in any artificial mixture. It is, I think, a conservative conclusion that for the normal infant, lactose and saccharose, within reasonable limits, are by no means dangerous; indeed, they are probably safer in the very early months than malt preparations would be. When nutritional disturbances do arise, these sugars must be reduced or temporarily entirely withdrawn, and if introduced again into the food must be introduced only with caution.

There is ample evidence that the sugars can initiate trouble, especially in the feeble and those who have previously suffered from nutritional disturbances. Exactly how they do so is not clearly understood. The process is usually spoken of as fermentation, but the irritative and poisonous products of this have not been isolated. Von Bokay, Escherich and others, have incriminated the lower fatty acids formed from the carbohydrates. Certainly the lower fatty acids are in excess in the diarrheal stools, but whether they come from the sugars or the fats cannot be determined. Whether the effect is direct from products of sugar disintegration or indirect perhaps by action on bacterial growth, the result is the same. The food substances, especially the fat, are poorly absorbed, there is a loss of sodium and potassium salts as a result of the excessive intestinal secretions, so that a negative balance of these substances results and there is an excessive ammonia content in the urine.

I should like to postpone consideration of some of the other effects, including the pyrogenic effect, of the sugars, especially lactose, until the salts are discussed, because of their close association together in whey, which has been in the last few years accorded a prominent place in the production of nutritional disturbances of infancy. Mention, however, should be made of the carbohydrates other than the sugars because of their general employment during the latter part of the first year and of their beneficial effect even in early infancy. Of their *modus operandi*, little accurate is known. That they act to a degree like sugars is undoubtedly true, but clinical, and to a certain extent chemical, testi-

mony is to the effect that they have another influence. An infant may maintain his weight, neither gaining nor losing for many days or weeks, when only diluted milk and sugar are given to him. If then a small amount of cereal is added, improvement in general condition and in weight may take place at once. On a milk and milk-sugar mixture an infant may be losing calcium and magnesium. If a cereal is added, the negative balance becomes a positive one and may continue positive even if the sugar be entirely withdrawn. The beneficial influence is perhaps to be found in the constant slight fermentation and acid formation that results. Klotz has shown that a small amount of lactic acid by mouth had clearly an influence in improving the absorption and utilization of organic and inorganic compounds.

There is the thought that perhaps cereals made from the whole grain may have an additional value, but while this is suggested by the influence of polished rice on the production of beri-beri, it is a suggestion only.

As to the injurious effects of an excess of properly cooked cereal, we know very little in this country. The obscure condition known to the Germans as *"Mehlnährschaden,"* with its disastrous outcome, is a clinical picture unknown to us. It is undoubtedly in part the result of hunger and nitrogenous and salt starvation, but whether the excess of cereal may also have a share in its production, is quite unknown.

The mineral metabolism of infants has been studied first to observe the effect of the increase or decrease of the mineral constituents, and second, as the means of determining the beneficial or harmful influence exerted by an alteration in the quantity or quality of the food. For in the ultimate analysis it is by the response of the mineral metabolism that we judge of the value of a food. It is the most sensitive indicator that we possess, and as such it is universally employed. There is, however, the very great disadvantage that under normal circumstances its behavior is very little known. There can be no doubt that normally, some of each of the mineral constituents is retained; yet in the literature can be found less than a half dozen experiments on breast-fed infants with complete, positive balances, and an equally small number on those artificially fed. In the great majority of metabolism experiments, on supposedly normal infants that have been published, one or more of the minerals has been excreted in greater amount than it was ingested. And, even when the balance of one mineral in a series of observations has been positive, the actual amount of it retained has been found to vary within extremely wide limits. The quantity that one considers should be retained is a question of personal belief and not one of demonstrated fact. For many decisions I believe that one period is not sufficient, but that two consecutive periods closely agreeing should be employed, and this, so far as I am aware, has practically never been done. Nor has it

been shown, except very rarely, that two periods may closely agree. Perhaps it is true that the minerals are not continuously or regularly retained. It is much more probable that our experiments are not planned so that we can demonstrate this. For there are a good many possible sources of error. The infants are rarely normal infants, and the conditions under which the experiments are made are not normal. The observations have, in many instances, been too short, and the periods of collection of excreta not sharply differentiated. The urine may always be sharply separated. The stools seldom are, and there is the chance that too little or too much may be included in collecting. In the case of substances that are largely excreted by the intestines this fact may alter the meaning of the whole experiment. Furthermore, the change from one diet to another is often made too abruptly and the experiment begun immediately on the change without opportunity for the infant to become adjusted to the new conditions. A subsequent experiment on the same diet might give a very different picture. Thus, with a great increase in the nitrogen or of the mineral constituents of the food, there may be an excessive retention of these for several days, the retained amount, however, becoming less and less until a point is reached, not much if any, above what it was on a much lower diet. Conversely, on a change to an insufficient diet there may be a great loss of nitrogen and salts; but as L. F. Meyer has demonstrated, this may be only for a time. The infant accustoms himself to a much lower level of metabolism and may even retain, in small quantity, nitrogen and salts, when losing weight. An early determination of his chemical balance would have given a totally erroneous impression of what the ultimate result would be, and one would have thought that he could go on losing minerals *ad infinitum*. It has been common to obtain one or two sets of figures and draw far-reaching conclusions from these which more careful observation would show to be quite unjustified. The literature is full of such conclusions. To explain some of these apparent contradictions it has been assumed that the infant possesses depots or stores of minerals that he may draw on during the first year at time of need, and that his body is therefore richer in some elements than it will subsequently be. This has not been proven except for iron, which, it is well known, his liver holds in excess. With this exception, from the time of birth until old age, the body becomes poorer and poorer in water and contains more and more salts.

The mineral metabolism of the artificially-fed differs greatly from that of the breast-fed infant. A comparison between the two is, therefore, well nigh impossible. The infant receiving cow's milk with its greater salt content, lives on a higher plane of mineral metabolism than does the one receiving breast milk. He absorbs 60 per cent. of the total

ash and retains only about 15 per cent., while the breast-fed child utilizes to the full his opportunities and absorbs 80 per cent. of the ash and retains 40 to 50 per cent. In the majority of instances this excessive salt intake undoubtedly does no harm; the surplus is not absorbed or is merely eliminated.

It is to the earthy alkalies and the alkaline bases that attention has chiefly been directed during the last few years. I have previously indicated the influence that the various foods may have on them. Sodium and potassium are usually well retained, unless severe diarrhea is present, due to any cause, and excess of fat or an excess of sugar. Under such circumstances they are lost, and the loss is badly borne and cannot indefinitely be continued. When all available alkalies have been drawn on, the infant breaks down his own tissue to furnish more of these substances, which is an explanation, for a part at least, of the excessive nitrogen excretion under such conditions. When diarrhea ceases and the intake is sufficient, a positive balance is rapidly instituted.

The metabolism of calcium has been largely studied on account of its close relationship to rickets and tetany. Calcium is so largely excreted by the bowel that it is impossible to say how much is absorbed, plays a part in the organism and is then excreted by the intestine, either because it is in excess or because, as in the case of rickets, the body cannot utilize it. This is also true of magnesium and to a much less extent of sodium and potassium. I have considered in detail the factors causing a retention and loss of calcium and the part played by protein, fat and carbohydrate. But in the study of the metabolism of rickets, these have rarely, if ever, been heeded. To cite a specific instance: In one study an infant on milk and cereal water was considered rachitic because he had a loss of calcium, and another fed on milk and malt-soup was considered non-rachitic because he retained calcium. In view of the work of Usuki and Stolte especially, the metabolism of rickets and tetany must be rewritten.

It was Finkelstein who first developed the conception that the sugar and salts of cow's milk, in the proportion in which they exist in cow's whey, were productive of much harm to the artificially fed infant, and were the cause of many, if not most, of the disturbances of nutrition. He emphasized that foods rich in whey were those on which infants developed their unfavorable symptoms, and that they were only cured by a diet in which cow's whey composed a minimum or from which it was excluded altogether. Finkelstein's contention seemed supported by Meyers' *"Austauschversuch,"* in which he fed to the same infant human whey and cow's fat and casein, and later cow's whey and human fat and casein. When the human whey was given, the infant's digestion was normal and he gained weight. When cow's whey was given, he lost

weight and had marked diarrhea. This experiment was claimed to prove the unfavorable influence of cow's whey. Stolte has criticized the conclusions drawn from it. He pointed out that the proportion of fat, protein and calcium was improper for the production of formed stools when cow's whey was given, while when human whey was given, there was ingested at the same time fat and calcium from the curd, in exactly the right proportion to produce formed stools.

It has been a fact generally known for many years that infants with acute nutritional disturbances excrete sugar in the urine when receiving milk of any kind. This is usually lactose. Such infants have more or less fever at the same time. From clinical observations Finkelstein and Meyer came to the conclusion that the sugar and salts that were allowed to reach the tissues of the body unchanged by reason of the diseased intestinal wall had a toxic and distinctly pyrogenic action. Contrary as was this belief to the general conception of the causation of fever, it obtained support from the experiments of Schaps. Schaps injected dilute solutions of lactose and sodium chlorid subcutaneously and obtained a perfectly definite and more or less characteristic temperature rise, beginning four to six hours after the injection, reaching the maximum in eight to twelve hours and becoming normal again in twenty-four.

Since these results were published in 1906 a considerable literature, containing the results of a great number of experiments by different observers, chiefly in Germany, has grown up around the subject of sugar fever and salt fever. Febrile reactions have been obtained many times in different ways and a number of ingenious hypotheses have been proposed to explain the method of production of the fever.

In order to judge whether the results obtained are applicable to the question of infant-feeding and prove the dependence of fever and other untoward symptoms on sugars and salts taken in the cow's milk, let us consider how these experiments have been conducted. The sugars and salts have been given by mouth and by subcutaneous injection to normal infants and those with nutritional disturbances. When normal infants have taken by mouth at one time as much as 30 grams of sugar or even more, no fever results. At least this is the consensus of opinion of most of those who have experimented with them; and even when the huge doses were employed for the determination of tolerance, no mention was made of fever by Grosz, Nobécourt, Terrien, Keller and others.

With sick infants it is different. They will react, but by no means regularly; less than 50 per cent. will do it. The temperature rise is not usually high; indeed, it is usually only slight, and it is somewhat delayed. The fever is found as often after large doses of glucose and saccharose, as after lactose and nearly as often after maltose. The

quantity that produces this reaction is, moreover, very large, 30 grams at one time, as much as the infant would otherwise take in the whole day.

It is difficult to see how such experiments can be expected to have any bearing on the question of infant-feeding or to prove the pyrogenic effect of lactose in the proportion in which it is found in cow's milk. They show unmistakably that concentrated sugar solutions have a bad effect on sick infants and this has long been known. More than this they cannot do.

Similarly with the various salts with which most of the experiments have been performed. Normal children do not usually respond with fever. Those who have been or are ill do so. But to produce fever, even with the sick, an amount is necessary that would at once indicate the impossibility of drawing any practical conclusions so far as nutritional disturbances are concerned. Indeed, doubt, and a very substantial doubt, is at once thrown on the part that these substances are claimed to play in such conditions. Thus infants of 3½ kilos and less have been given in a day 5½ grams of sodium chlorid, or 12 grams of sodium phosphate, 5 grams of sodium bromid, 10 grams of calcium lactate, 10 grams of calcium acetate and other substances in like proportion. The quantity at one dose has been 3 grams and sometimes more. It is only fair to ask, as Salge has done, what such experiments are designed to investigate and prove, even if fever, collapse, vomiting, diarrhea, hyperglycemia, mellituria and great loss of weight are produced. These studies are toxicological studies and have no bearing on the nutrition of infants. It is no wonder that febrile reaction occurs after giving at one dose in concentrated solution, six, eight or ten times as much of a substance as would be ingested under ordinary circumstances in a day and in a very dilute form. It is not at all improbable that similar or perhaps more disastrous results would follow the ingestion of a similar proportion of the other food ingredients provided they could be given at one time.

Injection experiments have seemed to offer more suggestive results. Schaps obtained fever regularly with minute quantities of sugar and salt in healthy and sick infants when given hypodermatically. Gofferjé, Möllhausen, Rietschel, Meyer and Schloss and many others had the same results. Weiland and Tjulpin were not able to produce fever and Friberger produced it in only one-third of his experiments. But the negative results were disregarded on account of the preponderance of the positive ones. The subject has been studied with great zeal, and the greater activity of sodium in combination with the halogens and the inhibiting effect of the divalent bases on the influence of the monovalent bases presumably established. But carefully conducted animal experiments lend no support to these views. Helmholz and Schultz in this

country, independently, investigated the effect of sugar and salt solutions on rabbits. Helmholz could show no pyrogenic influence for salts nor could Schlutz for sugars.

The studies of Wechselmann with salvarsan injections by which he showed that a febrile reaction frequently followed the use of distilled water if not immediately sterilized, and that the febrile reaction was absent if sterilization closely followed distillation, offered another field for inquiry. So also did the studies of the Lister Institute of Preventive Medicine in London, where it was demonstrated that salt solution or water is not free from pyrogenic properties even after all organisms have been destroyed by heat. Samelson, therefore, made a series of experiments with children less than 3 months of age, when they are supposed to be most likely to react. He used 20 to 80 c.c. of an 0.8 per cent. sodium chlorid solution freshly distilled and freshly sterilized, in all, seventeen times. No fever was ever produced and none of the other symptoms usually following injections. Fever was frequently produced when ordinary distilled and sterilized water was employed. The results that Bendix obtained were even more instructive. He injected seventeen infants with 50 c.c. of a 0.75 per cent. solution of salt and produced fever fifteen times. He then found that the water that had been used had been distilled the evening before and not been sterilized until twelve hours later. He therefore repeated his experiments, using freshly distilled and freshly sterilized water, and produced no fever and no symptoms in any single case. It appears, therefore, that there is no satisfactory proof that sugar or salt hypodermatically has a pyrogenic effect, and that experimental evidence that would show that the sugars and salts of the whey are responsible for fever and the chain of constitutional symptoms associated with it, is lacking. It may be that they act indirectly in injuring the cells of the intestinal tract so that other substances, perhaps bacterial, are absorbed. It may be that they act in a variety of other ways, but their own direct and damaging influence has not been proved, and has been, undoubtedly, greatly overemphasized.

The reasons for the difficulties or the failures with artificial feeding are at times sufficiently apparent. At others no fault, so far as one's experience goes, can be found, and yet the result may be far from satisfactory. This is more apt to be true of methods designed to correct some existing disturbance than it is of those employed with the normal infant. What is the explanation of failure with these?

Biological reasons have been offered and the influence of the prevalent views of workers in biological laboratories is reflected in these reasons. I have already referred to Hamburger's views on *"arteigenes"* and *"artfremdes Eiweiss,"* and the effect that the latter might exert on the immature organism. This was when the distinction was drawn between

homologous and heterologous compounds. In recent years the idea of anaphylaxis has crept into the discussion. This has been equally incapable of shedding light on the ordinary problems of nutrition. The diatheses have, therefore, been called on. Here we enter a very large and indefinite field.

The conception of diatheses first arose in an endeavor to explain the different degree of susceptibility and the different resistance manifested toward infection. Now they are used in questions of nutrition to explain what cannot be accounted for on a purely chemical basis. These diatheses are not sharply defined. The "scrophulous diathesis" has gradually disappeared, its place to be taken, in the non-tuberculous cases, by the "exudative diathesis" of Czerny. A lymphatic diathesis has been described, a thymico-lymphatic, an arthritic and a neuropsychopathic. The French have a different classification from the Germans and no two authors agree. If a conception to one seems too narrow it is broadened by combining two diatheses, as in the neurolymphatic; and finally all possible constitutional abnormalities and predispositions have been massed together and called *"Oxypathie"* by Stoeltzner.

The only diathesis, except for the pathological status thymicolymphaticus, that rests on a tangible basis is the "exudative diathesis" of Czerny. It has been shown that infants exhibiting symptoms of this usually utilize their ingested fats less well than the average and that their symptoms are increased by fat; that they have frequently hyperglycemia and alimentary mellituria, even with a small carbohydrate intake, and that they show a marked tendency to retain salt and water in their tissues. It is a question, however, how much light this conception of diatheses has brought to the subject that now interests us; probably not much. It has certainly tended to confuse.

We are thus left without an adequate explanation for many difficulties and many failures. This gives an incentive for future work.

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ENGLISH CONFERENCE ON INFANT MORTALITY

An English-speaking Conference on the Prevention of Infant Mortality will be held in Caxton Hall, Westminster, London, on Monday morning, Monday afternoon and Tuesday morning, Aug. 4 and 5, 1913. The meetings will be held under the auspices of the (British) National Association for the Prevention of Infant Mortality and The Welfare of Infancy under the patronage of the King and Queen, and will convene immediately preceding the opening of the International Medical Congress.

A tentative program has been issued by the committee which indicates that the papers will consist largely of medical opinion. The subjects treated will be:

The responsibility of central and local authorities in infant and child hygiene.

The administrative control of the milk-supply.

The necessity for special education in infant hygiene.

Medical problems in infant nutrition.

Antenatal hygiene.

The president of the conference will be the Hon. John Burns, M. P., president for the Local Government Board. The chairman of the English Executive Committee is Sir Thomas Barlow and the secretary, Miss J. Halford, 4 Tavistock Square, London, W. C.

The American committee, in charge of the part to be taken by the United States and Canada, will furnish information to those desiring to attend the conference.

Dr. Henry L. Coit, chairman, 277 Mt. Prospect Avenue, Newark, N. J.

Dr. Philip Van Ingen, secretary, 125 East Seventy-First Street, New York City.